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Review Article

The role of Optical Coherence Tomography in Parkinsonism: A critical review

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ABSTRACT

Optical coherence tomography (OCT) has been evaluated as a tool to assess retinal changes in various neurodegenerative disorders. Parkinson's disease (PD), is a neurodegenerative disorder wherein dopaminergic deficiency results in some of the symptoms. As retina also has high concentration of dopamine, it would be of interest for both the clinician as well as the basic scientist to know if there is a correlation between the clinical features and the retinal changes. The objective of this review is to critically evaluate the literature and study the utility of OCT as a tool to evaluate retinal changes in PD.

1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder. The cardinal motor symptoms of PD include rest tremor, rigidity, bradykinesia, and postural instability [1]. In addition, several non-motor symptoms such as cognitive impairment, psychosis, depression, visual disturbances, autonomic dysfunction, sleep disturbances may emerge during the course of illness [2]. PD is the commonest cause of parkinsonism. Other Parkinsonian disorders include Progressive supranuclear palsy (PSP), Multiple system atrophy (MSA), dementia with Lewy bodies (DLB) and corticobasal degeneration (CBD). The term 'Atypical parkinsonism' has been used for these non-PD parkinsonian disorders [3]. Diagnosis of the parkinsonian disorders is usually based on clinical grounds and response to treatment. These neurodegenerative disorders substantially worsen the quality of life of the patients as well as their caregivers. Appropriate diagnosis and management can alleviate the burden of care to some extent. Several studies based on advanced neuroimaging, molecular genetics, neuropsychological evaluation have been carried out to identify imaging/genetic/clinical/cognitive biomarkers for the parkinsonian disorders. However, at present, there are no reliable diagnostic or prognostic biomarkers for these diseases.

Changes in the retinal morphology are well known in patients with PD [4]. Retina, like the basal ganglia has a high concentration of dopamine especially the amacrine cells and the ganglion cells [5]. Hence, alteration in retinal morphology may be used as a surrogate marker of disease progression. Several studies have used Optical coherence tomography (OCT), a non invasive technique which enables in-vivo imaging of the retina, to study the retinal histology in patients with PD [6]. If early dopamine dysfunction could be detected by imaging of the retina, OCT could serve as a potential biomarker for the early diagnosis and prognosis in PD. OCT has been used to evaluate various parameters corresponding to retinal morphology. In both ophthalmological and neurological disorders such as Optic Neuritis, Multiple Sclerosis (MS), Neuromyelitis Optica (NMO) etc., OCT has been used to assess thickness of the retinal nerve fibre layer (RNFL), central macula, inner and outer retinal layers, total and central macular volumes [7–11]. OCT has also been used in the assessment of vascularity and perfusion of the optic disc [12,13]. The results of the various studies of OCT in PD have been inconclusive. Differences in methodology, lack of standardisation in reporting, heterogeneous study populations and dearth of longitudinal studies are the various caveats in the interpretation of the results.

The objective of this article is to critically review various studies of OCT in PD and other parkinsonian disorders, to consolidate the information, to understand the various mechanisms which lead to OCT changes in PD and to identify areas which need further research.

2. Search strategy

We followed the pertinent criteria of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and searched the literature published in PUBMED database for the last 15 years using the following key words- "Parkinson's disease AND Optical Coherence Tomography", "Progressive supranuclear palsy AND Optical Coherence Tomography", "Multiple system atrophy AND Optical Coherence

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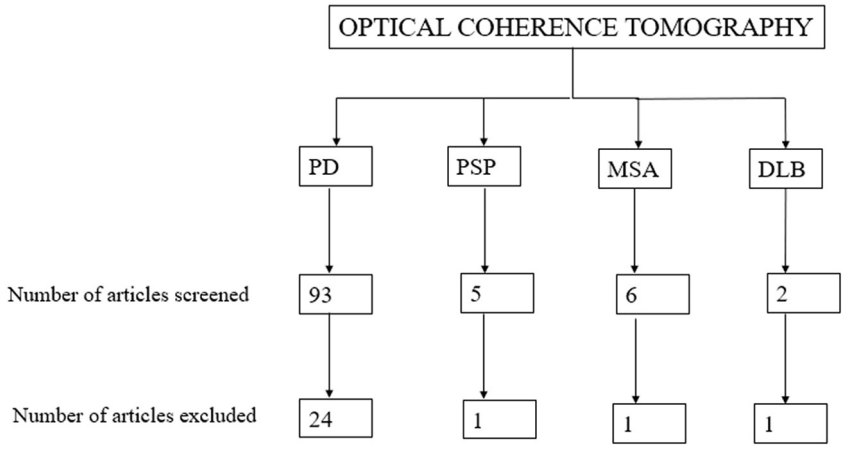

Fig. 1. Flow chart depicting search strategy.
Abbreviations: PD- Parkinson's disease, PSP- Progressive Supranuclear palsy, MSA- Multiple System Atrophy, DLB- Dementia with Lewy Bodies.

Tomography" and "Corticobasal degeneration AND Optical Coherence Tomography" (Fig. 1). The cross references from the articles were also screened. Some of the studies, which were not relevant to the article, were excluded after screening the titles, abstracts or full texts of articles obtained from the database. Studies were considered for review if: (1) they were either original or review articles, (2) full text was available in English. A total of 73 articles were included for the review.

3. Methods

RNFL thickness is measured around the optic disc at a diameter of 3.4 mm at temporal, nasal, superior and inferior quadrants (Fig. 2). The inner and outer retinal layer thickness are measured at fixed distances from the fovea in the temporal, nasal, superior and inferior quadrants. The outer retinal thickness is measured between outer border of the retinal pigment epithelium to the inner border of the outer plexiform layer (OPL), to include the inner segments, outer segments and the outer nuclear layer (ONL). The inner retinal layer (IRL) thickness is measured from the vitreoretinal interface to the inner border of the OPL. The OCT image of the macula with the retinal layers is depicted in Fig. 3. Some recent studies also utilised the segmentation technique to analyse the different layers of retina and automated software programs

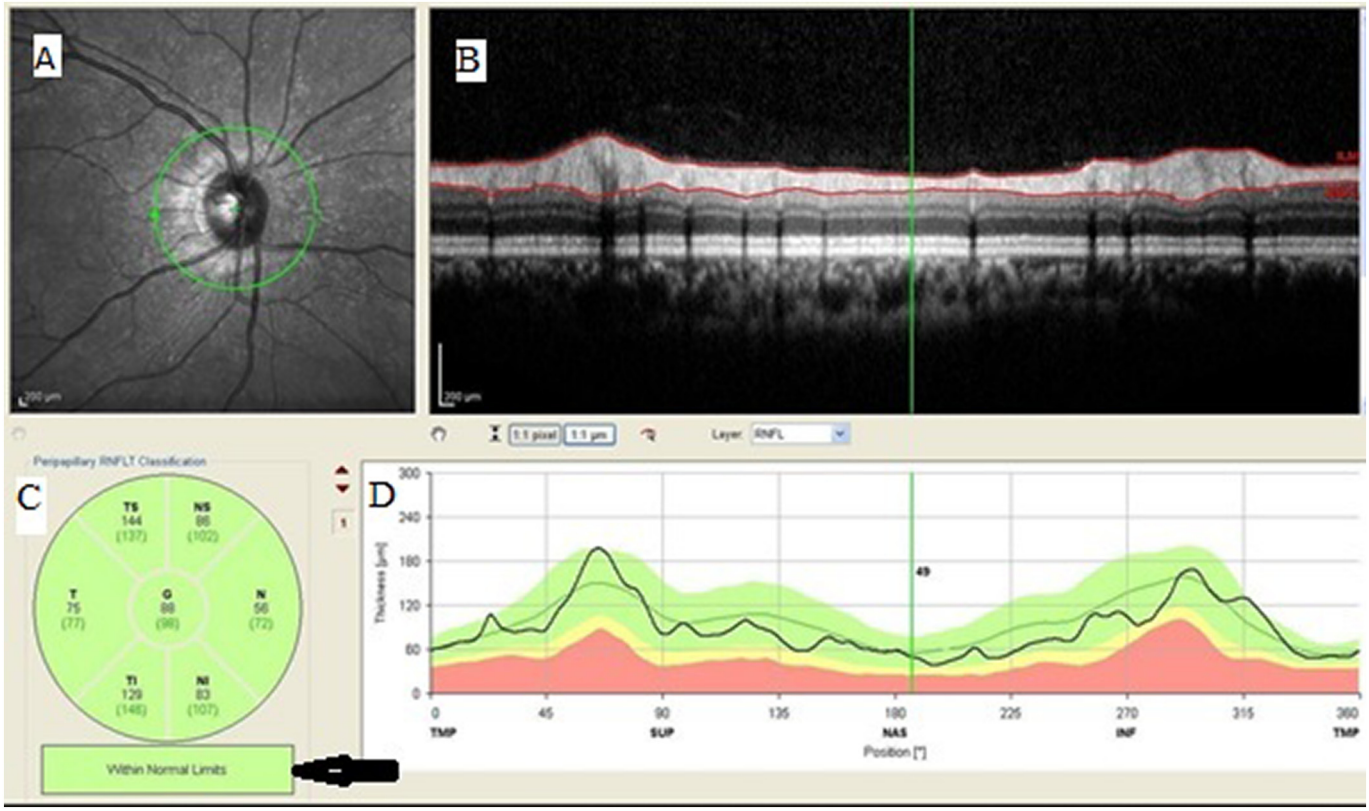

Fig. 2. Spectral Domain-OCT of the right eye of a patient showing normal RNFL values in all regions. A) Infrared image of the peripapillary region showing the location of the circular scan (green circle) centered around the optic nerve (green cross). B) OCT image depicting the segmented RNFL (redline).C) RNFL thickness measurement in each sector of the subject with the normative control values within brackets. The black arrow shows that the overall RNFL value is within normal limits D) Plot showing the TSNIT (temporal, superior, nasal, inferior, temporal) graph (blackline) within normal limits.

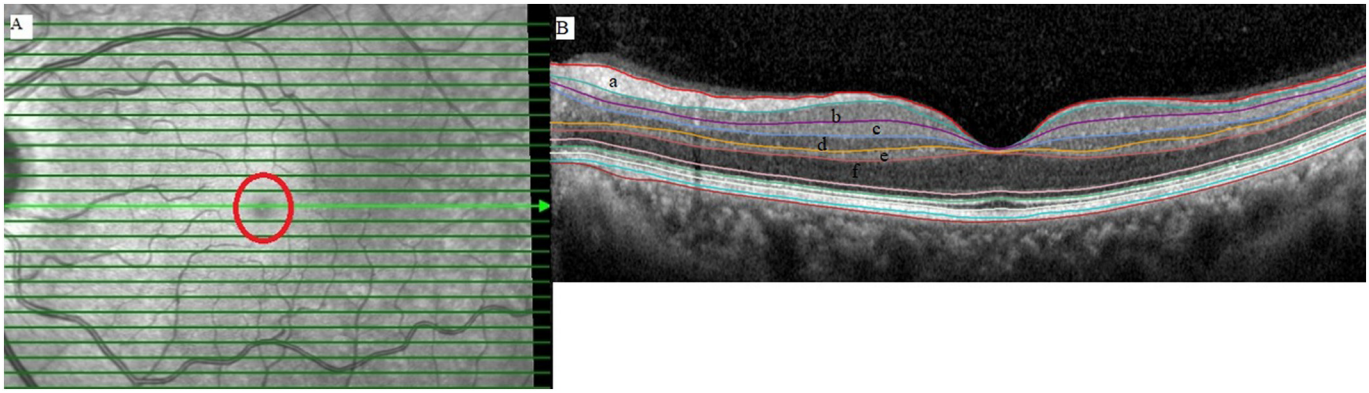

Fig. 3. Spectral Domain-OCT of the left eye of a patient showing normal macula. A) Infrared image of the macular region (red circle). B) Intra-retinal segmentation. Intra-retinal segmentation as performed by the software for the SPECTRALIS SD-OCT in the eye of a patient with Parkinson's disease. Layers are labelled: a- retinal never fibre layer (RNFL), b-ganglion cell layer (GCL), c- inner plexiform layer (IPL), d- inner nuclear layer (INL), e- outer plexiform layer (OPL), and f- outer nuclear layer (ONL).

(Heidelberg Engineering Inc., Heidelberg, Germany, Carl Zeiss Meditec, Inc., Dublin, CA, Cirrus 4000, Topcon, Tokyo, Japan), albeit different ones were used in most of the studies. Stratus, Cirrus, RTVue100, Zeiss 3000 unit and Spectralis were the various types of equipment used in different studies.

4. Results: (Table 1)

4.1. Parkinson's disease

4.1.1. Peripapillary RNFL

The studies of RNFL thickness in PD have yielded conflicting results. Several studies have reported RNFL thickness to be similar in patients and controls [14–23]. On the contrary, several other studies have shown decreased thickness of RNFL in PD [24–40]. Rohani et al. found that the Akinetic rigid subgroup of patients had thinner RNFL as compared to patients with tremor predominant type of PD [38]. The temporal quadrant was found to be thinner in some studies [25–27,36] which is also seen in some mitochondrial cytopathies.

Several groups have attempted correlation of RNFL with severity of PD [16,18,24,28,39–41]. Thickness of RNFL was found to have a negative correlation with the severity of PD in terms of both Unified Parkinson's disease Rating Scale (UPDRS) scores and Hoehn and Yahr (H & Y) stage. Contrary to this finding, several studies

Table 1
Studies using optical coherence tomography in Parkinson's Disease.

Inzelberg et al. [44]	P-10, C-10	57 ± 11	7 ± 4	NS	↓ in Inf and Tem	NS	NS	NS	NS
Atlintas et al. [54]	P-17, C-11	59.3 ± 12.8	4.6 ± 0.9	24.2 ± 3.5	↓ Sup and Nas	ND	↓	↓ Sup	↓ Tem Inf,Nas,
Hajee et al. [55]	P-24, C-17	63.5 ± 10.7	2.9	NS	NS	NS	NS	↓ Sup Inf	ND
Moschos et al. [30]	P- 16, C– 20	57 ± 11	7 ± 3	NS	↓ Inf Tem	NS	NS	NS	NS
Aeker et al. [15]	P-9, C-16	64	NA	NS	ND	ND	NS	ND	NS
Cubo et al. [42]	P-9, C-9	64.1 ± 12	8.4 ± 1.9	NS	NS	↓	NS	NS	NS
Archibald et al. [14]	P-32, C-14	71 ± 7.8	8.9 ± 5.6	25.7 ± 12.5	ND	ND	ND	NS	NS
Albrecht et al. [16]	P-40, C-35	61.2 ± 2	8.1 ± 0.8	35.7 ± 3.3	ND	ND	ND	NA	NA
Tsironi et al. [19]	P-24, C-24	66.6 ± 10.2	5.3 ± 3.5	ND	NS	NS	NS	NS	NS
Shrier et al. [50]	P-23, C-18	64.6 ± 7.5	NA	NA	NS	ND	↓	NA	NA
Rohani et al. [38]	P-27, C– 25	54.6 ± 10.4	6.9 ± 4	NA	↓ (all 4 quadrants)	NS	NS	NS	NS
Satue et al. [25]	P-100, C-100	64	5.25	NS	↓ supra and inferoTem	↓	NA	↓ Inf and Tem	↓ Inf
Kirbas et al. [26]	P- 42, C-40	59.3 ± 4.9	NA	NS	↓ Tem	NS	NS	NS	NS
Adam et al. [56]	P-14, C-14	68.6 ± 6.4	NA	NA	NS	NS	NS	↓ (Sup)	NS
La Morgia et al. [27]	P-43, C-86	65.6 ± 8.4	9.1 ± 6.5	25.9 ± 12.4	↓ Tem	NS	NS	NS	NS
Garcia Martin et al. [24]	P-46, C-33	70.7 ± 7.9	7.7	NS	↓ Tem Nas	↓	NS	↓ Tem Inf	↓ Inf Nas
Jimenez et al. [41]	P-52, C-50	67.8 ± 8.2	8.0 ± 6.8	23.0 ± 7.6	↓	NS	NS	NS	NS
Mailankody et al. [18]	P-30, C-30	53.4 ± 10.6	5.3 ± 4.1	30.5 ± 14.8	ND	↓	Increased	ND	↓ Inf Nas
Roth et al. [4]	P-97, C-32	68.8 ± 8.1	7.2	19 ± 10	ND	NA	ND	ND	↓ ONL + PRL
Jagan Pillai et al. [17]	P-20,C-34	62.6 ± 9.5	NA	23 ± 10.6	ND	NA	ND	NA	NA
Chorostecki et al. [23]	P-52, C-24	65.8 ± 10.6	6.4	NA	ND	NA	↓	↓ IPL INL	Higher OPL vol
Lee et al. [22]	P-61,C-30	69.6 ± 7.1	NA	26.4 ± 13.5	ND	ND	ND	↓ INL	ND
Bambo et al. [13]	P-155,C-91	67.33	2–19	NA	↓ Inf	NS	NS	NS	NS
Ucak et al. [46]	P-30,C-30	68.5 ± 7.63	4.87 ± 4.07	15.26 ± 4.10	↓ Sup Inf	ND	ND	↓ GCL	NA IPL
Sari et al. [32]	P-54,C-54	66.62 ± 8.71	5.12	NA	↓ Inf temp	NA	NA	↓ GCL-PL	NA
Bayhan et al. [31]	P-20,C-30	NA	NA	NA	↓ Nas	NA	NA	↓ GCL	NA
Bittersohl et al. [20]	P-108,C-165	NA	NA	NA	ND	↓	ND	NS	NS
Pilat et al. [43]	P-25,C-25	60.79 ± 9.24	NA	NA	↓	NA	NA	ND	Increased OPL ↓ ONL PRL
Aydin et al. [34]	P- 25, C– 29	70	4	24	↓ Global	NS	NA	NA	NA
L J Ma et al. [37]	P- 37, C– 42	60.43 ± 8.4	3	21.54 ± 11.49	↓ (Avg)	NS	↓	NA	NA
Gulmez et al. [35]	P- 41, C– 35	59.64 ± 9.94	4	NA	↓ (Avg)	NA	NA	NA	NA
Unlu et al. [36]	P- 58, C– 30	NA	NA	NA	↓ Tem SuperoTem	NS	NS	↓	High OPL Vol
Yavas et al. [33]	P- 44, C– 21	NA	NA	NA	↓	NA	NA	NA	NA
Matlach et al. [39]	P- 30, C– 40	64.1 ± 8.3	9.8 ± 6.9	41.0 ± 9.9	↓ Sup	NA	NA	NS	NA
Moschos et al. [40]	P- 31, C– 25	67.8 ± 3.9	NA	NA	↓ Sup Tem	NA	NA	↓	NA
Ahn et al. [57]	P-49, C-54	68.9 ± 9.1	NA	NA	NA	NA	NA	↓NFL, GCL IPL	NS

[16,27,28,34,39,40,42–45] found no correlation with the duration, severity or stage of the disease.

Moreno Ramos and Ucak et al. found RNFL to correlate with the Mini Mental Status Examination (MMSE) scores [46,48]. Lee et al. found that patients with hallucinations had a thinner RNFL as compared to patients without [22]. On the contrary, Kopal et al. found no difference between patients with and without visual hallucinations [49].

Shrier et al. suggested interocular asymmetry in the retina of patients with PD [50]. Some studies [27,42,43] revealed thinner RNFL on the side contralateral to the more affected side. On the contrary, Matlach, et al. found thinner RNFL on the side ipsilateral to the affected side [39].

Based on the measurement of thickness of RNFL in levodopa users and non-users, several studies proposed a protective role for levodopa [21,51,52]. Yavas et al. assessed the optic nerve head in addition to the RNFL thickness [33]. Thickness of the RNFL, rim area and volume of the optic nerve head were greater in patients on treatment with levodopa as compared to patients on treatment with dopamine agonist. They concluded that levodopa was more protective than dopamine agonist [33].

The progressive decrease in the thickness of RNFL has been demonstrated in some recent longitudinal studies [37,53]. Progressive thinning of RNFL, especially in the superotemporal and the temporal sectors, was accompanied by progressive visual dysfunction in patients with PD as compared to age matched controls [53].

4.1.2. Central macular thickness (CMT)

Patients with PD had decreased CMT as compared to the control group [18,24,25,37,42]. However, many other studies did not find any significant difference in the CMT when they compared patients with healthy controls [36,44,50,54,55]. Atlintas et al. and Mailankody et al. found a significant negative correlation between CMT and UPDRS motor score [18,54].

4.1.3. Total macular volume (TMV)

Studies on TMV in patients with PD have yielded contradictory findings. Some groups reported a significantly lower mean TMV in patients as compared to controls [23,37,50,54]. Certain other studies have found the macular volumes to be comparable between the patients and controls [14,16,17,20,22,45,46]. On the contrary, Mailankody et al. found TMV to be higher in the patients as compared to the controls. Authors hypothesised that this could represent cell swelling which is seen in early stage of cell death [18].

4.1.4. Retinal thickness

Thickness of the IRL was significantly decreased in patients with PD as compared to controls in some of the studies [24,25,54–56] whereas it was not significantly different from those of controls in some other studies [15,18,39,45]. The Ganglion cell layer and inner plexiform layer (IPL) were found to be thinner in patients as compared to healthy controls [32,46,57]. Bayhan et al. found thinning of macular Ganglion cell complex in patients with PD [31].

Altintas et al. reported a correlation between IRL thickness and disease severity in PD according to the UPDRS scale [55]. Ahn et al. found a negative correlation between the inner retinal layer thickness and the H & Y stage [57].

In a study of 40 patients with PD and 35 healthy controls, Albrecht et al. found that the inner nuclear layer (INL), which is a component of the IRL, was thicker in patients with PD as compared to controls [16]. Contradictory to Albrecht et al., Chorostecki et al. reported a thicker OPL and thinner INL in their study [23]. Higher volume of OPL was also found by Unlu et al. [36]. They proposed that the thicker OPL was due to accumulation of alpha synuclein in that layer with support of animal studies [23,36,58]. ONL and Photoreceptor layers showed significant thinning in patients with PD as compared to healthy controls [45].

The zone around foveola at a distance of 0.75 to 1.5 mm was found to be remodelled in patients with PD as compared to healthy controls by Spund et al. [59]. As the zone is devoid of nerve fibre layer and has an overlap with the avascular foveal zone, oxidative mechanisms have been suggested as the cause for the remodelling. The same study group also proposed a mathematical model based on the shape and volume, symmetry and asymmetry, size and thickness of the fovea for discriminating patients with PD from healthy controls [60]. Pilat et al. also found foveal remodelling in the form of thickening of the central OPL and thinning of the nasal retinal pigment epithelium (RPE) [43]. Thinning of RPE was a novel finding reported for the first time in this study.

Mailankody et al. and Satue et al. found thinning of outer macula [18,25]. Trans synaptic degeneration of the cells in the ONL due to impaired dopaminergic transmission was proposed to explain the same [18,25].

The changes in the retina in patients with PD suggest vascular and dopaminergic mechanisms. Nevertheless, most of the studies are cross sectional and the results lack reproducibility.

5. Atypical parkinsonian disorders

5.1. Multiple system atrophy (MSA)

Thickness of RNFL in patients with MSA was found to be decreased in some studies [29,61,62] and was found to be similar to that of control by some other groups [16,63] Mendoza et al. performed cross sectional and longitudinal evaluation of 24 visually asymptomatic patients with MSA and found progressive thinning of global as well as inferior quadrant of RNFL which correlated with the disease severity. They also found progressive thinning of the ganglion cell complex in the macular region of patients with MSA. Patients with MSA have normal visual acuity and colour vision as compared to patients with PD. This difference in symptomatology could be due to the differential involvement of the Magnocellular (M)- ganglion cells in MSA and Parvocellular (P)- ganglion cells in PD. P cells which are seen predominantly in the macular region relay colour discrimination and visual acuity whereas the M cells which are seen around the optic nerve transmit motion detection and achromatic vision [64]. The findings of this study highlighted the difference in the pathophysiological retinal changes in MSA as compared to that of PD. The authors also noted the average annual thinning of RNFL and ganglion cell layer in patients with MSA [29]. The same group carried out autopsy studies on three patients and found that there was diffuse loss of ganglion cells in the eyes of patients compared to controls [65]. Both thickness of RNFL and perifoveal retina were found to be lower in patients with MSA P as compared to MSA C by Ahn et al. The perifoveal thickness also had a significant negative correlation with the severity of the disease [62]. The perifoveal macula was found to be thinner in patients with MSA compared to controls [16,63]. Schneider et al. reported that patients with MSA had thicker OPL and thinner ONL as compared to controls [47].

5.2. Progressive supranuclear palsy (PSP)

OCT studies in 15 patients with PSP, 40 patients with PD and 35 age matched controls revealed that the mean RNFL did not differ significantly between groups [16]. A study of 22 patients with PSP found that RNFL thickness was reduced in the inferior nasal and inferior temporal areas as compared to controls [66]. A significant reduction of the superior RNFL was found in patients with PSP as compared to patients with PD by another group [52]. The macular volume as well as the thickness of the macular sectors were found to be significantly decreased in the patients [52]. Due to the lack of correlation of the retinal findings with disease duration and severity, authors suggested that OCT could be used in the early diagnosis and in differentiation from PD [66].

In patients with PSP, the complex of retinal ganglion cell- and inner plexiform layer (IPL), the ONL and the mean paramacular thickness and volume were reduced. The ratio between the ONL and the OPL was found to be useful in differentiation of PSP from PD [16]. Thicker ONL was also found by Schneider et al. [47].

5.3. Dementia with Lewy bodies (DLB)

Moreno-Ramos et al. evaluated patients with Dementia with Lewy bodies, Alzheimer's disease, dementia associated with PD and cognitively normal controls (10 in each group). Thinner RNFL in patients with DLB as compared to patients in other groups was not statistically significant. However, there was significant correlation of RNFL with mental status examination [48].

5.4. Functional correlates of OCT parameters

Contrast sensitivity, pattern electroretinogram and Visual evoked potential were the functional assessments performed in different studies. Atlintas et al. found VEP latency to be inversely correlated with macular volume [54]. Kopal et al. reported that structural and functional changes in the retina had no role in genesis of visual hallucinations contradictory to the finding by Lee et al. [22,49]. A significant correlation between the structural changes of the retina and function was found by several groups [36,43,53,54,67,68]. Contrast sensitivity was found to have no correlation with IRL in one earlier study [56]. Nevertheless, contrast sensitivity was found to have the best correlation with the structural changes in a recent study by Polo et al. [69]. The latter study had a greater number of patients and controls when compared to the former one. The authors concluded that ganglion cell layer could be a reliable indicator for the functional alterations in PD [69–70].

6. Discussion

It has been more than 10 years since Inzelberg first applied OCT in patients with PD [44]. In spite of more than a decade of research, there is lack of consistency and reproducibility with regard to OCT data in PD. There are several unresolved challenges in the interpretation of OCT (Table 2). Nevertheless, OCT studies have contributed significantly to the understanding of pathophysiology of PD (Table 3).

Ahn et al. for the first time demonstrated an association of retinal thinning with nigral dopaminergic depletion with the help of Dopamine transporter Positron Emission Tomography (PET) [57]. Nevertheless, RNFL thickness and thickness of the macular layers have been found to be decreased in other neurological diseases such as Alzheimer's disease, Wilson's disease, Huntington's disease, Multiple sclerosis (MS) and Neuromyelitis Optica (NMO) [7–10,71–74]. So, thinning of RNFL and macular layer in PD appears to be a non-specific marker of degeneration rather than a finding specific for PD. Attributing it to dopaminergic loss may not be justified as loss of RNFL and macular thickness also happens in other diseases where dopaminergic loss does not occur.

The finding that a specific region around the fovea is remodelled in PD and that has overlap with the avascular zone suggests vascular mechanisms in the genesis of these changes. The same group quantified the capillary remodelling in the retina of patients with PD [75]. The decreased thickness of the choroid was found in patients with PD by Eraslan et al. and Moschos et al. [40,76]. Garcia Martin et al. found that thickness of the peripapillary choroid was greater in patients with PD in all zones as compared to that of controls [77]. Using a different OCT device with better accuracy for measurements of choroidal thickness and a larger sample size of 40 patients were the reasons cited by the authors for the difference in the results as compared to the study by Eraslan et al. Nevertheless, both studies support the concept of vascular disturbances in the pathogenesis of OCT changes as choroid is a highly vascular structure [40,76,77]. Kromer et al. found changes in the retinal vasculature especially the retinal veins in patients with PD using OCT [12]. On the contrary, Gulmez et al. found that the retinal vessel diameter in patients with PD was not different compared to that of controls [35]. Optic disc in patients with PD was found to have lower mean haemoglobin as compared to that of healthy controls [13].

Differential involvement of the retinal layers in PD and MSA found by Mendoza et al. suggest a difference in the mechanisms involved in the pathogenesis of these disorders [29]. The clinical finding of impaired contrast sensitivity and colour vision in PD as opposed to MSA support the possible involvement of metabolically active P ganglion cells in PD and inactive M ganglion cells in MSA. Involvement of temporal RNFL in PD which receives inputs from the P ganglion cells further supports the hypothesis [29,78,79]. Nevertheless, these findings need to be confirmed with larger and longer studies. The thicker ONL in patients with PSP and thicker OPL in patients with MSA could become a diagnostic feature if it is validated in larger groups of patients.

Deposition of alpha synuclein in inner layers of retina has been demonstrated by clinicopathological studies [80,81]. Animal studies have revealed alpha synuclein deposition in the OPL as well as IPL [58]. The involvement of temporal RNFL is a pattern which is also seen in mitochondrial optic neuropathies. (27). Alpha synuclein can lead to impairment of mitochondrial function. [82].

There is ambiguity and uncertainty regarding the correlation between OCT parameters and severity of the disease across different studies. Albrecht et al. hypothesised that lack of correlation suggests that retinal changes occur early in the disease and hence do not show correlation with progression of the disease [16]. This may help in the early differential diagnosis of the disease. Longitudinal study by Satue et al. does provide evidence for progression of OCT changes due to the disease [53]. Correlation of the OCT parameters with the stage and severity of the disease as found by several groups needs to be evaluated by more longitudinal studies. A recent study by Normando et al. demonstrated that rosiglitazone had a protective effect on the retinal ganglion cells in the rotenone induced rodent model of PD. The retinal layers were found to be thicker on day 20 after the rotenone administration and by an in vivo imaging technique called DARC (detection of apoptosing retinal cells), it was found that the thicker retinal layers corresponded with the increased apoptosis of retinal ganglion cells. Administration of liposome encapsulated rosiglitazone was found to produce retained dopaminergic cells in the substantia nigra in the rodent models. Changes in the OCT parameters preceded the histopathological changes of the striatum and substantia nigra. Objective demonstration of improvement with the drug using OCT suggests a potential role for the use of retinal imaging with OCT as a biomarker for future studies in PD [83].

Most of the studies did not report detailed ophthalmological assessments. The patients included in these studies were over the age of 50 years (Table 1). Meticulous ophthalmological evaluation would be required to diagnose concomitant ocular pathologies like glaucoma, age related macular degeneration, hypertensive retinopathy etc. which are common in the elderly population and could have been missed or overlooked.

The devices used were different in the various studies. There are

Table 2
Challenges in the interpretation of OCT.

Differences in the instruments used
Racial differences
Cross sectional studies
Heterogeneity of the study population with respect to age of the patients, duration and severity of the disease
Concomitant ocular pathologies may have been missed
The contribution of blood vessels to the thickness of Retinal nerve fibre layer not assessed
Lack of sufficient data regarding the effect of drug on retina
Lack of consistent and reproducible results across different studies

Table 3
Pathophysiological changes in the retinal layers in Parkinson's disease: Insight from OCT studies.

Observation	Interpretation
Thinning of the inner retinal layers which contain the dopaminergic amacrine cells [22–25,31,32,36,40,46,54–57]	Dopaminergic depletion [5]
Thicker outer plexiform layer [23,36,43]	Alpha synuclein deposition [80,81]
Thinner outer nuclear layer and photoreceptor layer [45]	Dopamine deficiency
Decreased thickness of temporal RNFL [25–27,36]	Mitochondrial toxicity [27]
Changes in the thickness of choroid and retinal vessel diameter [12,40,75–77]	Vascular disturbances

many studies which have compared the measurements of RNFL and macular thickness among different OCT instruments [84–87]. The study by Bock et al. found significant differences in absolute retinal nerve fibre layer measurements between the Stratus time domain OCT and Cirrus spectral domain OCT. [88]. They concluded that the instruments cannot be used interchangeably. Though Matlach et al. found a high degree of repeatability and consistency of measurements between RTVue 100 and Cirrus OCT devices, authors did report that the macular ganglion cell layer and RNFL were thicker when measured in RTVue [85]. Hence, difference in the instruments and their OCT specifications may act like confounders across the studies.

The various OCT parameters may also have certain racial differences. Knight et al. evaluated 284 subjects in a cross sectional observational study and found that significant racial differences exist in the RNFL thickness [89]. This reinforces that, the racial differences in the OCT parameters have to be considered and appropriate matching has to be done while recruiting the healthy controls.

An expert task force validated the OSCAR- IB quality control criteria for use of OCT in MS research and clinical trials. The criteria deal with the quality of the image, signal strength, fundus illumination and can pick up inaccuracies in the procedure if any [90,91]. Quality control of source data was not reported in most studies in PD.

An attempt has been made towards the standardisation in reporting OCT studies by International Multiple Sclerosis Visual (IMVISUAL) consortium in 2015 [92]. Advised Protocol for OCT Study Terminology and Elements recommendations (APOSTEL recommendations) have been developed to outline core information that should be provided when reporting quantitative OCT studies [92].

7. Lessons from OCT studies in NMO spectrum disorders

OCT studies in patients with NMO Spectrum Disorders with and without Optic neuritis led to the recognition of a novel retinal target in the pathophysiology of NMO spectrum disorder [93]. The contribution of blood vessels to the thickness of RNFL has also been identified by another elegant study in NMO spectrum disorder [94]. The caution required in the interpretation of 'thin RNFL' has been highlighted in this study and may be applicable to OCT research in other disorders as well. The contribution of blood vessel to RNFL thickness was not analysed in any of the studies in PD to the best of our knowledge.

8. Conclusion

The evidence from the various studies suggest a definite involvement of the retina in parkinsonian disorders. Nevertheless, the lack of consistent and reproducible results across different studies with respect to RNFL, CMT, IRL thickness suggest that the potential for retinal imaging with OCT to become a biomarker needs further exploration. With the current evidence, utility of OCT in Parkinsonian disorders is only in a research context and not in the bedside. Assessment of the thickness of the retina and its layers with histopathological confirmation will help in delineating the pathogenesis of various disorders.

9. Future directions

Selective and differential involvement of the different layers of the retina in PD and other parkinsonian disorders suggest that the focus of research should include the layers of retina around the macula in addition to the peripapillary RNFL. Longitudinal studies with large sample sizes are essential for attaining reliable and reproducible results. Histopathological analysis of the retinal layers will help not only to confirm the results, but also to elucidate the possible mechanisms which lead to these changes. This in turn may explain the pathogenesis of the various parkinsonian disorders.

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References

[1] J. Jankovic, Parkinson's disease: clinical features and diagnosis, J. Neurol. Neurosurg. Psychiatry 79 (4) (2008) 368–376.
[2] K.R. Chaudhuri, D.G. Healy, A.H. Schapira, National Institute for clinical excellence. Non-motor symptoms of Parkinson's disease: diagnosis and management, Lancet Neurol. 5 (3) (2006) 235–245.
[3] I. Litvan, What is an atypical parkinsonian disorder? in: I. Litvan (Ed.), Atypical Parkinsonian Disorders: Clinical and Research Aspects, Humana Press, New Jersey, 2005, pp. 1–9.
[4] M.B. Djamgoz, M.W. Hankins, J. Hirano, S.N. Archer, Neurobiology of retinal dopamine in relation to degenerative states of the tissue, Vis. Res. 37 (24) (1997) 3509–3529.
[5] C. Harnois, T. Di Paolo, Decreased dopamine in the retinas of patients with Parkinson's disease, Invest. Ophthalmol. Vis. Sci. 31 (11) (1990) 2473–2475.
[6] D. Huang, E.A. Swanson, C.P. Lin, J.S. Schuman, W.G. Stinson, W. Chang, et al., Optical coherence tomography, Science. 254 (5035) (1991) 1178–1181.
[7] L.J. Balcer, L.J. Balk, A.U. Brandt, P.A. Calabresi, E.H. Martinez-Lapiscina, R.C. Nolan, F. Paul, A. Petzold, S. Saidha, The international multiple sclerosis visual system consortium: advancing visual system research in multiple sclerosis, J. Neuroophthalmol. 38 (4) (2018 Dec) 494–501, https://doi.org/10.1097/WNO.0000000000000732.
[8] A.T. Waldman, G.T. Liu, A.M. Lavery, G. Liu, W. Gaetz, T.S. Aleman, B.L. Banwell, Optical coherence tomography and visual evoked potentials in pediatric MS, Neurol Neuroimmunol Neuroinflamm. 4 (4) (2017 Jun 5) e356, , https://doi.org/10.1212/NXI.0000000000000356.
[9] F.C. Oertel, H. Zimmermann, F. Paul, A.U. Brandt, Optical coherence tomography in neuromyelitis optica spectrum disorders: potential advantages for individualized monitoring of progression and therapy, EPMA J. 9 (1) (2017 Dec 22) 21–33, https://doi.org/10.1007/s13167-017-0123-5.
[10] Y. You, E.C. Graham, T. Shen, C. Yiannikas, J. Parratt, V. Gupta, J. Barton, M. Dwyer, M.H. Barnett, C.L. Fraser, S.L. Graham, A. Klistorner, Progressive inner nuclear layer dysfunction in non-optic neuritis eyes in MS, Neurol Neuroimmunol Neuroinflamm. 5 (1) (2017 Dec 15) e427, , https://doi.org/10.1212/NXI.0000000000000427.
[11] T. Oberwahrenbrock, G.L. Traber, S. Lukas, I. Gabilondo, R. Nolan, C. Songster, L. Balk, A. Petzold, F. Paul, P. Villoslada, A.U. Brandt, A.J. Green, S. Schippling, Multicenter reliability of semiautomatic retinal layer segmentation using OCT, Neurol Neuroimmunol Neuroinflamm. 5 (3) (2018 Mar 13) e449, , https://doi.org/10.1212/NXI.0000000000000449.
[12] R. Kromer, C. Buhmann, U. Hidding, M. Keserü, D. Keserü, A. Hassenstein, B. Stemplewitz, Evaluation of retinal vessel morphology in patients with Parkinson's disease using optical coherence tomography, PLoS One 11 (8) (2016 Aug 15) e0161136.
[13] Maria Pilar Bambo, Elena Garcia-Martin, Maria Satue, Susana Perez-Olivan, Silvia Alayon, Marta Gonzalez-Hernandez, Vicente Polo, Jose Manuel Larrosa and Manuel Gonzalez-De la Rosa Measuring hemoglobin levels in the optic disc of parkinson's disease patients using new colorimetric analysis software.
[14] N.K. Archibald, M.P. Clarke, U.P. Mosimann, D.J. Burn, Retinal thickness in

Parkinson's disease, Parkinsonism Relat. Disord. 17 (6) (2011) 431–436.
[15] G.D. Aaker, J.S. Myung, S. Kiss, Detection of retinal changes in Parkinson's disease with spectral-domain optical coherence tomography, Clin. Ophthalmol. 4 (2010) 1427–1432.
[16] P. Albrecht, A.K. Muller, M. Sudmeyer, S. Ferrea, M. Ringelstein, E. Cohn, Optical coherence tomography in parkinsonian syndromes, PLos One 7 (2012) e34891.
[17] J.A. Pillai, R. Bermel, A. Bonner-Jackson, A. Rae-Grant, H. Fernandez, J. Bena, S.E. Jones, J.P. Ehlers, J.B. Leverenz, Retinal nerve fiber layer thinning in Alzheimer's disease: a case-control study in comparison to normal aging, Parkinson's disease, and non-Alzheimer's dementia, Am. J. Alzheimers Dis. Other Dement. 31 (5) (2016 Aug) 430–436.
[18] P. Mailankody, R. Battu, A. Khanna, A. Lenka, R. Yadav, P.K. Pal, Optical coherence tomography as a tool to evaluate retinal changes in Parkinson's disease, Parkinsonism Relat. Disord. 21 (10) (2015 Oct) 1164–1169.
[19] E.E. Tsironi, A. Dastiridou, A. Katsanos, E. Dardiotis, S. Veliki, G. Patramani, et al., Perimetric and retinal nerve fiber layer findings in patients with Parkinson's disease, BMC Ophthalmol. 12 (54) (2012).
[20] D. Bittersohl, B. Stemplewitz, M. Keserü, C. Buhmann, G. Richard, A. Hassenstein, Detection of retinal changes in idiopathic Parkinson's disease using high-resolution optical coherence tomography and Heidelberg retina tomography, Acta Ophthalmol. 93 (7) (2015 Nov) e578–e584.
[21] Z.J. Yang, J. Wei, C.J. Mao, J.R. Zhang, J. Chen, X.Y. Ji, J.Y. Liu, Y. Shen, K.P. Xiong, J.Y. Huang, Y.P. Yang, C.F. Liu, Retinal nerve fiber layer thinning: a window into rapid eye movement sleep behavior disorders in Parkinson's disease, Sleep Breath. 3 (2016 Jun).
[22] J.Y. Lee, J.M. Kim, J. Ahn, H.J. Kim, B.S. Jeon, T.W. Kim, Retinal nerve fiber layer thickness and visual hallucinations in Parkinson's disease, Mov. Disord. 29 (1) (2014 Jan) 61–67.
[23] J. Chorostecki, N. Seraji-Bozorgzad, A. Shah, F. Bao, G. Bao, E. George, V. Gorden, C. Caon, E. Frohman, Bhatti MTKhan O˙, Characterization of retinal architecture in Parkinson's disease, J. Neurol. Sci. 355 (1–2) (2015 Aug 15) 44–48.
[24] E. Garcia-Martin, D. Rodriguez-Mena, M. Satue, C. Almarcegui, I. Dolz, R. Alarcia, et al., Electrophysiology and optical coherence tomography to evaluate Parkinson disease severity, Invest. Ophthalmol. Vis. Sci. 55 (2) (2014) 696–705.
[25] M. Satue, E. Garcia-Martin, I. Fuertes, S. Otin, R. Alarcia, R. Herrero, et al., Use of Fourier-domain OCT to detect retinal nerve fiber layer degeneration in Parkinson's disease patients, Eye (Lond). 27 (4) (2013) 507–514.
[26] S. Kirbas, K. Turkyilmaz, A. Tufekci, M. Durmus, Retinal nerve fiber layer thickness in Parkinson disease, J. Neuroophthalmol. 33 (1) (2013) 62–65.
[27] C. La Morgia, P. Barboni, G. Rizzo, M. Carbonelli, G. Savini, C. Scaglione, et al., Loss of temporal retinal nerve fibers in Parkinson disease: a mitochondrial pattern? Eur. J. Neurol. 20 (1) (2013) 198–201.
[28] M. Eraslan, S.Y. Balci, E. Cerman, A. Temel, D. Suer, N.T. Elmaci, Comparison of optical coherence tomography findings in patients with primary open-angle glaucoma and parkinson disease, J. Glaucoma 25 (7) (2016 Jul) e639–e646.
[29] C.E. Mendoza-Santiesteban, J.A. Palma, J. Martinez, L. Norcliffe-Kaufmann, T.R. Hedges III, H. Kaufmann, Progressive retinal structure abnormalities in multiple system atrophy, Mov. Disord. 30 (14) (2015 Dec) 1944–1953.
[30] M.M. Moschos, G. Tagaris, I. Markopoulos, I. Margetis, S. Tsapakis, M. Kanakis, et al., Morphologic changes and functional retinal impairment in patients with Parkinson disease without visual loss, Eur. J. Ophthalmol. 21 (1) (2011) 24–29.
[31] H.A. Bayhan, S. Aslan Bayhan, N. Tanık, C. Gürdal, The association of spectral-domain optical coherence tomography determined ganglion cell complex parameters and disease severity in Parkinson's disease, Curr. Eye Res. 39 (11) (2014 Nov) 1117–1122.
[32] E.S. Sari, R. Koc, A. Yazici, G. Sahin, S.S. Ermis, Ganglion cell-inner plexiform layer thickness in patients with Parkinson disease and association with disease severity and duration, J. Neuroophthalmol. 35 (2) (2015 Jun) 117–121.
[33] G.F. Yavas, O. Yilmaz, T. Küsbeci, F. Oztürk, The effect of levodopa and dopamine agonists on optic nerve head in Parkinson disease, Eur. J. Ophthalmol. 17 (5) (2007 Sep-Oct) 812–816.
[34] T.S. Aydin, D. Umit, O.M. Nur, U. Fatih, K. Asena, O.Y. Nefise, Y. Serpil, Optical coherence tomography findings in Parkinson's disease, Kaohsiung J. Med. Sci. 34 (3) (2018 Mar) 166–171.
[35] D. Gulmez Sevim, M. Unlu, S. Sonmez, M. Gultekin, C. Karaca, A. Ozturk Oner, Retinal vessel diameter obtained by optical coherence tomography is spared in Parkinson's disease, Int Ophthalmol. 34 (2019 April) 813–819.
[36] M. Unlu, D. Gulmez Sevim, M. Gultekin, C. Karaca, Correlations among multifocal electroretinography and optical coherence tomography findings in patients with Parkinson's disease, Neurol. Sci. 39 (3) (2018 Mar) 533–541.
[37] L.J. Ma, L.L. Xu, C.J. Mao, Y.T. Fu, X.Y. Ji, Y. Shen, J. Chen, Y.P. Yang, C.F. Liu, Progressive changes in the retinal structure of patients with Parkinson's disease, J. Park. Dis. 8 (1) (2018) 85–92.
[38] M. Rohani, A.S. Langroodi, S. Ghourchian, K.G. Falavarjani, R. Soudi, G. Shahidi, Retinal nerve changes in patients with tremor dominant and akinetic rigid Parkinson's disease, Neurol. Sci. 34 (5) (2013) 689–693.
[39] J. Matlach, M. Wagner, U. Malzahn, I. Schmidtmann, F. Steigerwald, T. Musacchio, J. Volkmann, F. Grehn, W. Göbel, S. Klebe, Retinal changes in Parkinson's disease and glaucoma, Parkinsonism Relat Disord. 56 (2018 Nov) 41–46.
[40] M.M. Moschos, I.P. Chatziralli, Evaluation of choroidal and retinal thickness changes in Parkinson's disease using spectral domain optical coherence tomography, Semin. Ophthalmol. 33 (4) (2018) 494–497.
[41] B. Jiménez, F.J. Ascaso, J.A. Cristóbal, J. López del Val, Development of a prediction formula of Parkinson disease severity by optical coherence tomography, Mov. Disord. 29 (1) (2014) 68–74.
[42] E. Cubo, R.P. Tedejo, V. Rodriguez Mendez, M.J. López Peña, Trejo Gabriel Y Galán JM., Retina thickness in Parkinson's disease and essential tremor, Mov. Disord. 25 (14) (2010) 2461–2462.
[43] A. Pilat, R.J. McLean, F.A. Proudlock, G.D. Maconachie, V. Sheth, Y.A. Rajabally, I. Gottlob, In vivo morphology of the optic nerve and retina in patients with Parkinson's disease, Invest. Ophthalmol. Vis. Sci. 57 (10) (2016 Aug 1) 4420–4427.
[44] R. Inzelberg, J.A. Ramirez, P. Nisipeanu, A. Ophir, Retinal nerve fiber layer thinning in Parkinson disease, Vis. Res. 44 (24) (2004) 2793–2797.
[45] N.M. Roth, S. Saidha, H. Zimmermann, A.U. Brandt, J. Isensee, A. Benkhellouf-Rutkowska, M. Dornauer, A.A. Kühn, T. Müller, P.A. Calabresi, F. Paul, Photoreceptor layer thinning in idiopathic Parkinson's disease, Mov. Disord. 29 (9) (2014) 1163–1170.
[46] T. Ucak, A. Alagoz, B. Cakir, E. Celik, E. Bozkurt, G. Alagoz, Analysis of the retinal nerve fiber and ganglion cell - Inner plexiform layer by optical coherence tomography in Parkinson's patients, Parkinsonism Relat Disord. 31 (2016) 59–64.
[47] M. Schneider, H.P. Müller, F. Lauda, H. Tumani, A.C. Ludolph, J. Kassubek, E.H. Pinkhardt, Retinal single-layer analysis in parkinsonian syndromes: an optical coherence tomography study, J. Neural Transm. (Vienna) 121 (1) (2014 Jan) 41–47.
[48] T. Moreno-Ramos, J. Benito-León, A. Villarejo, F. Bermejo-Pareja, Retinal nerve fiber layer thinning in dementia associated with Parkinson's disease, dementia with Lewy bodies, and Alzheimer's disease, J. Alzheimers Dis. 34 (3) (2013) 659–664.
[49] Aleš Kopal, Eva Mejzlíková, Jana Lízrová Preiningerová, David Brebera, Olga Ulmanová, Edvard Ehler, Jan Roth, Changes of retina are not involved in the genesis of visual hallucinations in parkinson's disease, Parkinsons Dis. (2015) 709191.
[50] E.M. Shrier, C.R. Adam, B. Spund, S. Glazman, I. Bodis-Wollner, Interocular asymmetry of foveal thickness in Parkinson disease, J Ophthalmol. (2012) 728457.
[51] A. Sen, B. Tugcu, C. Coskun, C. Ekinci, S.A. Nacaroglu, Effects of levodopa on retina in Parkinson disease, Eur. J. Ophthalmol. 24 (1) (2014 Jan-Feb) 114–119.
[52] D. Gulmez Sevim, M. Unlu, M. Gultekin, C. Karaca, M. Mirza, G.E. Mirza, Evaluation of retinal changes in progressive Supranuclear palsy and Parkinson disease, J. Neuroophthalmol. 12 (2017 Dec).
[53] M. Satue, M.J. Rodrigo, J. Obis, E. Vilades, H. Gracia, S. Otin, M.I. Fuertes, R. Alarcia, J.A. Crespo, V. Polo, J.M. Larrosa, L.E. Pablo, E. Garcia-Martin, Evaluation of progressive visual dysfunction and retinal degeneration in patients with Parkinson's disease, Invest. Ophthalmol. Vis. Sci. 58 (2) (2017 Feb 1) 1151–1157.
[54] O. Altintaş, P. Işeri, B. Ozkan, Y. Cağlar, Correlation between retinal morphological and functional findings and clinical severity in Parkinson's disease, Doc. Ophthalmol. 116 (2) (2008) 137–146.
[55] M.E. Hajee, W.F. March, D.R. Lazzaro, A.H. Wolintz, E.M. Shrier, Bodis-Wollner, et al., Inner retinal layer thinning in Parkinson disease, Arch. Ophthalmol. 127 (6) (2009) 737–741.
[56] C.R. Adam, E. Shrier, Y. Ding, S. Glazman, I. Bodis-Wollner, Correlation of inner retinal thickness evaluated by spectral-domain optical coherence tomography and contrast sensitivity in Parkinson disease, J. Neuroophthalmol. 33 (2) (2013) 137–142.
[57] J. Ahn, J.Y. Lee, T.W. Kim, E.J. Yoon, S. Oh, Y.K. Kim, J.M. Kim, S.J. Woo, K.W. Kim, B. Jeon, Retinal thinning associates with nigral dopaminergic loss in de novo Parkinson disease, Neurology 91 (11) (2018 Sep 11) e1003–e1012 doi: 10.1212.
[58] G.C. Martínez-Navarrete, J. Martín-Nieto, J. Esteve-Rudd, A. Angulo, N. Cuenca, Alpha synuclein gene expression profile in the retina of vertebrates, Mol. Vis. 13 (2007 Jun 18) 949–961.
[59] B. Spund, Y. Ding, T. Liu, I. Selesnick, S. Glazman, E.M. Shrier, I. Bodis-Wollner, Remodeling of the fovea in Parkinson disease, J. Neural Transm. (Vienna) 120 (5) (2013 May) 745–753.
[60] Y. Ding, B. Spund, S. Glazman, E.M. Shrier, S. Miri, I. Selesnick, I. Bodis-Wollner, Application of an OCT data-based mathematical model of the foveal pit in Parkinson disease, J. Neural Transm. (Vienna) 121 (11) (2014 Nov) 1367–1376.
[61] M.D. Fischer, M. Synofzik, C. Kernstock, J. Dietzsch, R. Heidlauf, J. Schicks, K. Srulijes, S. Wiethoff, O. Menn, D. Berg, L. Schöls, U. Schiefer, Decreased retinal sensitivity and loss of retinal nerve fibers in multiple system atrophy, Graefes Arch. Clin. Exp. Ophthalmol. 251 (1) (2013 Jan) 235–241.
[62] J. Ahn, J.Y. Lee, T.W. Kim, Retinal thinning correlates with clinical severity in multiple system atrophy, J. Neurol. 14 (2016 Jul).
[63] John H. Pula, Vernon L. Towle, Victoria M. Staszak, Dingcai Cao, Jacqueline T. Bernard, Christopher M. Gomez, Retinal nerve fibre layer and macular thinning in spinocerebellar Ataxia and cerebellar multisystem atrophy, Neuroophthalmology. 35 (3) (2011 Jun) 108–114.
[64] L.C. Silveira, C.A. Saito, B.B. Lee, et al., Morphology and physiology of primate M- and P-cells, Prog. Brain Res. 144 (2004) 21–46.
[65] C.E. Mendoza-Santiesteban, J.A. Palma, I. Ortuño-Lizarán, N. Cuenca, H. Kaufmann, Pathologic confirmation of retinal ganglion cell loss in multiple system atrophy, Neurology. 88 (23) (2017 Jun 6) 2233–2235, https://doi.org/10.1212/WNL.0000000000004020.
[66] B. Stemplewitz, R. Kromer, E. Vettorazzi, U. Hidding, A. Frings, C. Buhmann, Retinal degeneration in progressive supranuclear palsy measured by optical coherence tomography and scanning laser polarimetry, Sci. Rep. 7 (1) (2017 Jul 13) 535.
[67] M. Kaur, R. Saxena, D. Singh, M. Behari, P. Sharma, V. Menon, Correlation between structural and functional retinal changes in Parkinson disease, J. Neuroophthalmol. 35 (3) (2015 Sep) 254–258.
[68] S. Miri, S. Glazman, L. Mylin, I. Bodis-Wollner, A combination of retinal morphology and visual electrophysiology testing increases diagnostic yield in Parkinson's disease, Parkinsonism Relat. Disord. 22 (Suppl. 1) (2016 Jan)

S134–S137.
[69] V. Polo, M. Satue, M.J. Rodrigo, S. Otin, R. Alarcia, M.P. Bambo, M.I. Fuertes, J.M. Larrosa, L.E. Pablo, E. Garcia-Martin, Visual dysfunction and its correlation with retinal changes in patients with Parkinson's disease: an observational cross-sectional study, BMJ Open 6 (5) (2016 May 6) e009658.
[70] E. Garcia-Martin, J.M. Larrosa, V. Polo, M. Satue, M.L. Marques, R. Alarcia, M. Seral, I. Fuertes, S. Otin, L.E. Pablo, Distribution of retinal layer atrophy in patients with Parkinson disease and association with disease severity and duration, Am J Ophthalmol. 157 (2) (2014 Feb) (470-478.e2).
[71] G. Coppola, A. Di Renzo, L. Ziccardi, F. Martelli, A. Fadda, G. Manni, P. Barboni, F. Pierelli, A.A. Sadun, V. Parisi, Optical coherence tomography in Alzheimer's disease: a meta-analysis, PLoS One 10 (8) (2015 Aug 7) e0134750.
[72] E. Salobrar-Garcia, I. Hoyas, M. Leal, R. de Hoz, B. Rojas, A.I. Ramirez, J.J. Salazar, R. Yubero, P. Gil, A. Triviño, J.M. Ramirez, Analysis of retinal peripapillary segmentation in early alzheimer's disease patients, Biomed Res Int. (2015) 636548.
[73] J.N. Ratchford, M.E. Quigg, A. Conger, T. Frohman, E. Frohman, L.J. Balcer, P.A. Calabresi, D.A. Kerr, Optical coherence tomography helps differentiate neuromyelitis optica and MS optic neuropathies, Neurology. 73 (4) (2009 Jul 28) 302–308.
[74] C. Andrade, J. Beato, A. Monteiro, A. Costa, S. Penas, J. Guimarães, F.F. Reis, C. Garrett, Spectral-domain optical coherence tomography as a potential biomarker in Huntington's disease, Mov. Disord. 31 (3) (2016 Mar) 377–383.
[75] Shahnaz Miri, Eric M. Shrier, Sofya Glazman, Yin Ding, Ivan Selesnick, Piotr B. Kozlowski, Ivan Bodis-Wollner, The avascular zone and neuronal remodeling of the fovea in Parkinson disease, Ann Clin Transl Neurol. 2 (2) (2015 Feb) 196–201.
[76] M. Eraslan, E. Cerman, S. Yildiz Balci, H. Celiker, O. Sahin, A. Temel, D. Suer, Elmaci N. Tuncer, The choroid and lamina cribrosa is affected in patients with Parkinson's disease: enhanced depth imaging optical coherence tomography study, Acta Ophthalmol. 94 (1) (2016 Feb) e68–e75.
[77] E. Garcia-Martin, L.E. Pablo, M.P. Bambo, R. Alarcia, V. Polo, J.M. Larrosa, E. Vilades, B. Cameo, E. Orduna, T. Ramirez, M. Satue, Comparison of peripapillary choroidal thickness between healthy subjects and patients with Parkinson's disease, PLoS One 12 (5) (2017 May 16) e0177163.
[78] C. La Morgia, L. Di Vito, V. Carelli, M. Carbonelli, Patterns of retinal ganglion cell damage in neurodegenerative disorders: parvocellular vs magnocellular degeneration in optical coherence tomography studies, Front. Neurol. 8 (2017 Dec 22) 710.
[79] C. La Morgia, F.N. Ross-Cisneros, A.A. Sadun, V. Carelli, Retinal ganglion cells and circadian rhythms in Alzheimer's disease, Parkinson's disease, and beyond, Front. Neurol. 8 (2017 May 4) 162.
[80] T.G. Beach, J. Carew, G. Serrano, C.H. Adler, H.A. Shill, L.I. Sue, M.N. Sabbagh, H. Akiyama, N. Cuenca, Arizona Parkinson's Disease Consortium, Phosphorylated α-synuclein-immunoreactive retinal neuronal elements in Parkinson's disease subjects, Neurosci Lett. 571 (2014 Jun 13) 34–38.
[81] I. Bodis-Wollner, P.B. Kozlowski, S. Glazman, S. Miri, α-Synuclein in the inner retina in parkinson disease, Ann. Neurol. 75 (6) (2014 Jun) 964–966.
[82] M.P. Giannoccaro, C. La Morgia, G. Rizzo, V. Carelli, Mitochondrial DNA and primary mitochondrial dysfunction in Parkinson's disease, Mov. Disord. 32 (3) (2017 Mar) 346–363.
[83] E.M. Normando, B.M. Davis, L. De Groef, S. Nizari, L.A. Turner, N. Ravindran, M. Pahlitzsch, J. Brenton, G. Malaguarnera, L. Guo, S. Somavarapu, M.F. Cordeiro, The retina as an early biomarker of neurodegeneration in a rotenone-induced model of Parkinson's disease: evidence for a neuroprotective effect of rosiglitazone in the eye and brain, Acta Neuropathol Commun. 4 (1) (2016 Aug 18) 86.
[84] U.E. Wolf-Schnurrbusch, L. Ceklic, C.K. Brinkmann, M.E. Iliev, M. Frey, S.P. Rothenbuehler, V. Enzmann, S. Wolf, Macular thickness measurements in healthy eyes using six different optical coherence tomography instruments, Invest. Ophthalmol. Vis. Sci. 50 (7) (2009 Jul) 3432–3437.
[85] J. Matlach, M. Wagner, U. Malzahn, W. Göbel, Repeatability of peripapillary retinal nerve fiber layer and inner retinal thickness among two spectral domain optical coherence tomography devices, Invest. Ophthalmol. Vis. Sci. 55 (10) (2014 Sep 16) 6536–6546.
[86] E.S. Lee, S.Y. Kang, E.H. Choi, J.H. Kim, N.R. Kim, G.J. Seong, C.Y. Kim, Comparisons of nerve fiber layer thickness measurements between stratus, cirrus, and RTVue OCTs in healthy and glaucomatous eyes, Optom. Vis. Sci. 88 (6) (2011 Jun) 751–758.
[87] M.T. Leite, H.L. Rao, R.N. Weinreb, L.M. Zangwill, C. Bowd, P.A. Sample, A. Tafreshi, F.A. Medeiros, Agreement among spectral-domain optical coherence tomography instruments for assessing retinal nerve fiber layer thickness, Am J Ophthalmol. 151 (1) (2011 Jan) 85–92.e1.
[88] M. Bock, A.U. Brandt, J. Dörr, C.F. Pfueller, S. Ohlraun, F. Zipp, F. Paul, Time domain and spectral domain optical coherence tomography in multiple sclerosis: a comparative cross-sectional study, Mult. Scler. 16 (7) (2010 Jul) 893–896, https://doi.org/10.1177/1352458510365156.
[89] O.J. Knight, C.A. Girkin, D.L. Budenz, M.K. Durbin, Feuer WJ; cirrus OCT normative database study group. Effect of race, age, and axial length on optic nerve head parameters and retinal nerve fiber layer thickness measured by cirrus HD-OCT, Arch. Ophthalmol. 130 (3) (2012) 312–318.
[90] P. Tewarie, L. Balk, F. Costello, A. Green, R. Martin, S. Schippling, A. Petzold, The OSCAR-IB consensus criteria for retinal OCT quality assessment, PLoS One 7 (4) (2012) e34823doi: 10.1371.
[91] S. Schippling, L.J. Balk, F. Costello, P. Albrecht, L. Balcer, P.A. Calabresi, J.L. Frederiksen, E. Frohman, A.J. Green, A. Klistorner, O. Outteryck, F. Paul, G.T. Plant, G. Traber, P. Vermersch, P. Villoslada, S. Wolf, A. Petzold, Quality control for retinal OCT in multiple sclerosis: validation of the OSCAR-IB criteria, Mult. Scler. 21 (2) (2015 Feb) 163–170, https://doi.org/10.1177/1352458514538110.
[92] Andrés Cruz-Herranz, Lisanne J. Balk, Timm Oberwahrenbrock, Philipp Albrecht, et al., The APOSTEL recommendations for reporting quantitative optical coherence tomography studies, Neurology. 86 (24) (2016 Jun 14) 2303–2309.
[93] F.C. Oertel, J. Kuchling, H. Zimmermann, C. Chien, F. Schmidt, B. Knier, J. Bellmann-Strobl, T. Korn, M. Scheel, A. Klistorner, K. Ruprecht, F. Paul, A.U. Brandt, Microstructural visual system changes in AQP4-antibody-seropositive NMOSD, Neurol Neuroimmunol Neuroinflamm. 4 (3) (2017 Feb 22) e334.
[94] F.C. Oertel, H. Zimmermann, J. Mikolajczak, M. Weinhold, E.M. Kadas, T. Oberwahrenbrock, F. Pache, J. Bellmann-Strobl, K. Ruprecht, F. Paul, A.U. Brandt, Contribution of blood vessels to retinal nerve fiber layer thickness in NMOSD, Neurol Neuroimmunol Neuroinflamm. 4 (3) (2017 Apr 18) e338.