In Vivo Morphology of the Optic Nerve and Retina in Patients With Parkinson's Disease

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Purpose. To investigate optic nerve (ON) and macular morphology in patients with Parkinson's disease (PD) using spectral-domain optical coherence tomography (SD-OCT).

Subjects. Twenty-five participants with PD (19 males and 6 females; mean age 60.79; SD ± 9.24) and 25 sex-, age-, ethnicity-, and refraction-matched healthy controls.

Methods. A high-resolution SD-OCT device was used to acquire scans in 25 participants with PD (mean age 60.79; ± SD 9.24) and 25 sex-, age-, ethnicity-, and refraction-matched healthy controls. Main outcome measures included optic nerve head parameters (disc/cup diameters/areas, cup/rim volumes, cup depth, cup/disc ratio; peripapillary retinal nerve fiber layer [ppRNFL] thickness), retinal thickness (in inner and outer annuli around the foveal center) and thickness of individual retinal layers.

Results. Our study showed significant ppRNFL thinning in PD patients in all quadrants ($P < 0.05$) associated with a shallower optic cup ($P = 0.03$) as compared with controls. Foveal remodelling with retinal thinning (nasal and temporal segments in both annuli; and superior segment in outer annulus; $P < 0.05$), foveal pit widening ($P = 0.05$), central outer plexiform layer (OPL) thickening ($P < 0.001$), and nasal RPE thinning ($P < 0.001$) was also found in PD. The differences were more obvious in hemiretinae related to the predominantly affected cerebral hemisphere. Changes were more pronounced in advanced stages and longer PD duration.

Conclusions. Optic nerve changes in PD are likely to be caused by primary neurodegeneration. Central retinal thinning, pit widening, central OPL thickening, and RPE thinning indicate foveal remodelling. Specific changes of the fovea and thinning of individual retinal layers, correlating with disease severity and duration, indicate that ON and retinal changes have potential to be used as biomarkers for PD.

Key words: Parkinson's disease, OCT, foveal remodelling

Parkinson's disease (PD) is one of the most common neurodegenerative disorders[1] associated with progressive loss of dopaminergic neurons in the nigrostriatal complex[2] leading to various motor symptoms, such as postural instability, tremor, muscular rigidity, and nonmotor symptoms including depression, psychosis, and sleep disorders.[2] Patients with PD have a variety of abnormal visual functions[3] such as reduced color and contrast vision.[4]

Increased incidence of glaucoma of approximately 23.7% has been found among PD patients in contrast to an incidence of glaucoma of 2% to 12% in healthy age-matched controls.[5] In this study, the diagnosis of glaucoma was based on glaucoma-like visual field deficits (9 of 17 patients) on Humphrey visual field testing and increased cup/disk ratio over 0.8 (1 of 17 patients) detected on ophthalmoscopy. No fundus photos or optical coherence tomography (OCT) were reported. Interestingly, in this study, with the exception of one patient (2.6%), all had normal IOP. Changes therefore may not be associated with elevated IOP but could be related to neuronal degeneration intrinsic to PD. Recent OCT studies describe peripapillary RNFL (ppRNFL) thinning in PD patients.[6,7] To our knowledge, objective optic nerve (ON) parameters such as disc/cup diameters/areas, cup/rim volumes, cup depth, cup/disc ratio have not been reported using OCT in PD.

Histologic studies have shown the presence of dopaminergic neurons in the retinal inner plexiform layer (IPL), ganglion cell layer (GCL), outer plexiform layers (OPL), and the outer segment (OS) of photoreceptors.[8] Reduced amplitudes and increased latencies of visual evoked potentials have been reported in PD.[9–12] Electroretinography showed reduced a- and b-wave amplitudes indicating that retinal alterations are likely to contribute to changes in visual function.[10,13] Moreover, Ikeda et al.[11] found a delay in the light peak in electrooculography reflecting reduced function of RPE.

Recent OCT studies investigating retinal structure in PD showed retinal and central macular thinning as well as RNFL thinning.[14–16] The foveal pit was found to be thinner and broader in PD,[17] which correlated to a smaller sized foveal avascular zone.[18]

Individual retinal layers have been investigated in very few studies using segmentation analysis, with controversial results. Variances in findings may arise from differences in segmentation methodology, type of OCT machines, selection criteria of patients or statistical approaches. Albrecht et al.,[19] using

manual segmentation of the macular region, described thinning of the combined GCL, IPL, and ONL as well as thickening of the inner nuclear layer (INL). Garcia-Martin et al.[15] confirmed these findings but additionally found RNFL thinning in the macular area using automated segmentation analysis. The authors acknowledged possible errors due to layer recognition.[20] In contrast, Schneider et al.[21] have not found any significant changes in individual retinal layers (from RNFL to OPL) in PD participants.

Intraocular asymmetry of inner and outer retinal layers between the right and left eye has also been described in PD patients.[22]

Because retinal changes have been found to correlate with disease duration and severity[14,15] retinal morphology has been suggested as a possible biomarker of PD.[16] Neurological deficits usually start and are more severe in one side of the patient's body (and opposite cerebral hemisphere). Consequently, it would be interesting to compare the hemiretinae corresponding to the predominantly affected cerebral hemisphere (i.e., the contralateral nasal hemiretina and the ipsilateral temporal hemiretina to the hemisphere) as compared with the opposite hemiretinae.

In the present study, we carefully selected participants without ophthalmological disease. Our aims were to: (1) investigate whether there are ON changes in PD and, if so, whether they correspond to typical glaucomatous changes, (2) corroborate changes in individual retinal layer thicknesses using manual segmentation, (3) compare the hemiretinae corresponding with the predominantly affected cerebral hemisphere (the contralateral nasal hemiretina and the ipsilateral temporal hemiretina to the hemisphere) as compared with the opposite hemiretinae, (4) investigate correlations between OCT and clinical parameters such as visual acuity (VA) and duration and severity of disease.

Methods

Subjects

In this prospective observational study, 25 patients with PD were compared with 25 sex-, age-, ethnicity- (Caucasian), and refraction-matched healthy controls (Supplementary Table S1). The diagnosis of idiopathic PD was established based on the UK Brain Bank Criteria.[9] The Hoehn & Yahr grade (HY) was used to quantify the disease stage. The more severely affected side was determined from history of onset and severity of neurological symptoms.

All subjects had standard ophthalmologic examination including refraction, best-corrected visual acuity (BCVA), refraction, orthoptic examination, slit-lamp examination, IOP measurements (IOP was < 21 mm for all subjects), and dilated fundoscopy. Participants with PD and control subjects had otherwise no known ophthalmic pathology, no previous eye surgery, and no other known neurological disease, diabetes, or active cardiovascular disease. Demographic data are shown in the Supplementary Table S1.

The study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee. Informed consent was obtained from all participants.

Optical Coherence Tomography

A high resolution spectral-domain (SD) OCT (Copernicus, wavelength = 850 nm, theoretical axial resolution of 3.0 μm; Optopol Technology S.A., Zawiercie, Poland) was used to acquire tomograms ($7 \times 7 \times 2$ mm, 75 b-scans, 743 a-scans per b-scan) centered on fovea and ON. To avoid possible bias during image analysis, random numbers were allocated to OCT scans to mask the examiner to the diagnoses (PD or control) during image analysis.

Optic Nerve Head Analysis. Standard ONH measurements including cup, disc, and rim diameters, areas and volumes, and the thickness of the RNFL were measured using an automated algorithm (Figs. 1A, 1B).

To minimize any inaccurate measurements by the software the disc margins, position of the internal limiting membrane (ILM) and RNFL were adjusted manually (Figs. 1A, 1B). Peripapillary RNFL (ppRNFL) thickness was measured within the temporal, superior, nasal, and inferior quadrants of an annulus with internal diameter of 2.4 mm and width of 0.4 mm (default settings; Fig. 1B).

Foveal Analysis. *Semi-Automated Analysis of Total Retinal Thickness.* Retinal thickness and RNFL thickness in the macular area were measured using a semiautomated method. The manufacturer's software was used for flattening the b-scans along the RPE. The position of the ILM, the outer limit of the RNFL and the RPE were delineated using automated algorithms in the software and corrected manually to minimize segmentation inaccuracies. The retinal and RNFL thickness were measured in three standard circular zones as defined by Early Treatment Diabetic Retinopathy Study[23] (central annulus [1 mm], inner annulus [1–3 mm], and outer annulus (3–6 mm]) and the inner/outer annuli were separated into four quadrants (superior, inferior, temporal, and nasal).

Manual Retinal Segmentation Analysis of Individual Retinal Layers of Foveal b-Scan. For segmentation layer analysis a single central horizontal flattened b-scan was selected at the deepest point of the foveal pit where the OS of photoreceptors was thickest, indicating specialization (i.e., elongation) of photoreceptors at the pit.

Analysis was performed using an ImageJ macro (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) with the retinal layer borders positioned manually by locating points, which were fitted with a spline fit. The borders were used to calculate thickness measurements of the RNFL, GCL, IPL, INL, OPL, ONL, inner segment (IS), OS, contact cylinder (CC), and RPE layers (Fig. 1C). The position of the retinal layers was measured across the whole scan. For statistics thickness measurements in the central point, paracentral area (averaged thickness of each layers from 250-μm nasally to 250-μm temporarily from the center), nasal/temporal areas (averaged thickness of each layers from 500–2000 μm from the center, nasally, and temporarily, respectively) were used (Fig. 1C).

The foveal pit depth was analyzed using the same macro and the lateral distance between the largest nasal and temporal retinal thicknesses points of the ILM (foveal width); axial distance from the line connecting the largest nasal and temporal retinal thickness points to the bottom of the pit (pit depth), and pit area (area, limited by ILM and pit width) were measured (Fig. 1D).

To establish the differences of the hemiretinae corresponding to more and less severely affected cerebral hemisphere we compared ppRNFL thickness, total retinal thickness, and individual layer thicknesses in nasal and temporal hemiretinae of both eyes.

Statistical Analysis

Statistical analysis was performed using SPSS software version 16.0 (SPSS, Inc., Chicago, IL, USA). Optic nerve head (ONH) and macular parameters were normally distributed (Shapiro–Wilk test). Parameters of ONH and macula were analyzed using linear mixed-models. Bonferroni correction was used for post

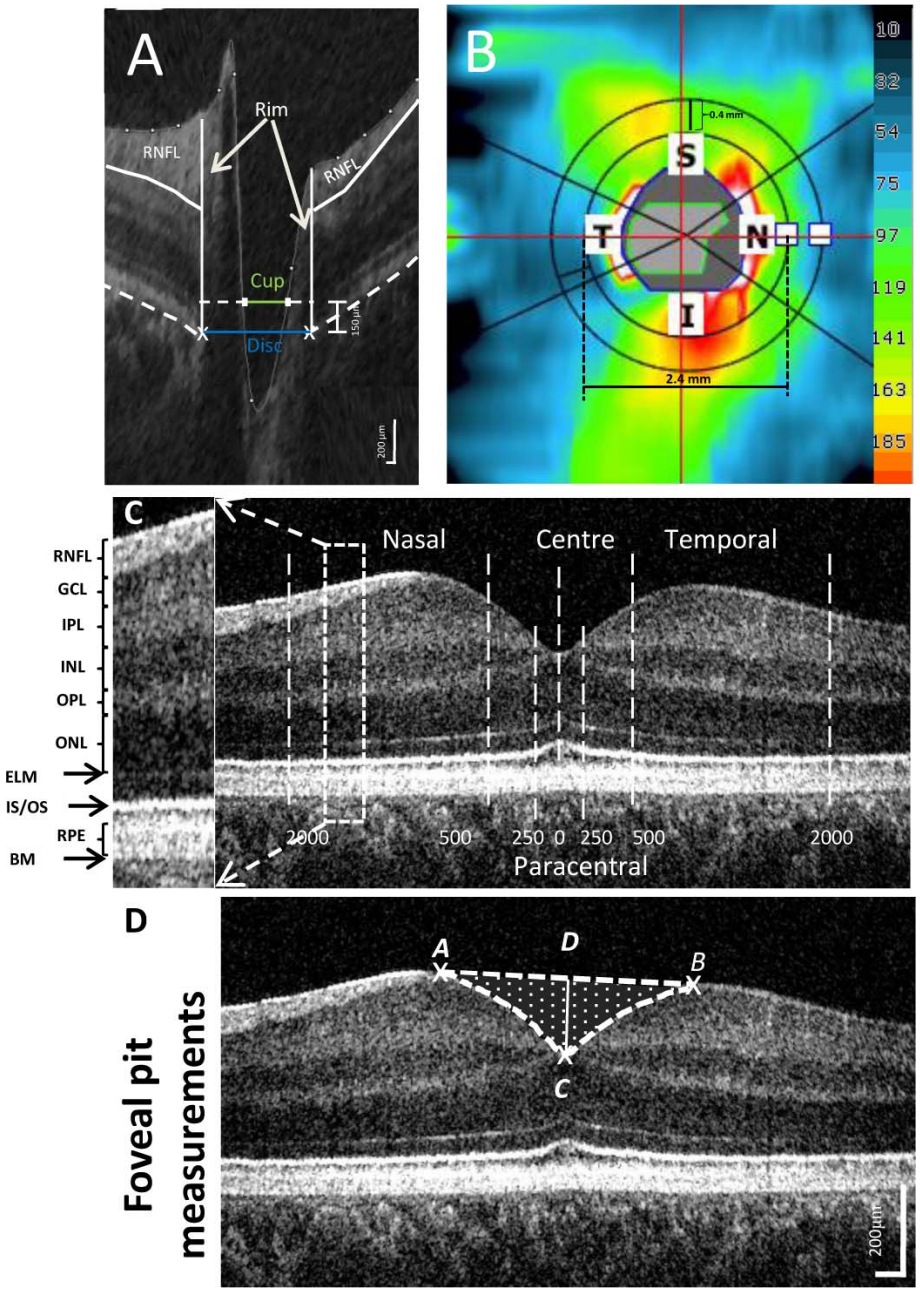

Figure 1. Optical coherence tomography analysis of the optic disc (**A**, **B**) and horizontal SD-OCT b-scan image of the fovea (**C**, **D**) of the healthy participant. (**A**) A b-scan centered on the optic disc; the disc diameter (interval between the edges of Bruch's membrane) was automatically identified; positioning of the disc (defined by the edges of Bruch's membrane) was checked and manually corrected if needed; cup diameters and volumes were defined from the ILM falling posterior to a plane 150-µm anterior to the plane of the disc), the rim was defined as tissue within the disc edges anterior to the same plane (150-µm anterior to the plane of the disc); maximal cup depth was measured using a perpendicular line to the line between the cup diameter and deepest point of the cup, the delineation of the RNFL was corrected manually. (**B**) Retinal nerve fiber layer thickness map shows the data measured within the temporal (T), superior (S), nasal (N), and inferior (I) quadrants of an annulus with internal diameter of 2.4 mm and width of 0.4 mm. The color code indicates thicknesses between 10 and 185 µm. (**C**) The position of the different retinal layers on an OCT b-scan image of the macula area (enlarged view shown on the *left*). The thickness of the layers was measured in the center of the fovea, in the paracentral area (from 250-µm nasally to 250-µm temporally) and nasally and temporally (from 500–2000 µm). (**D**) The foveal pit parameters: *AB*, foveal width, i.e., the lateral distance measured between the most prominent nasal and temporal points on ILM; *DC*, pit depth, corresponding to the axial distance from the line connecting the most prominent nasal and temporal ILM points to the bottom of the pit; *dotted area*, pit area, limited by ILM and pit width. ONL, outer nuclear layer; ELM, external limiting membrane; BM, Bruch's membrane.

hoc multiple comparisons (comparing "ipsilateral" and "contralateral" retinal parts in PD patients). Correlations between OCT parameters and clinical characteristics were made using Spearman's rank correlation. *P* less than or equal to 0.05 was considered statistically significant.

Results

Optic Nerve Head Morphology

Visual inspection of ONH scans did not reveal any differences between PD participants and control subjects.

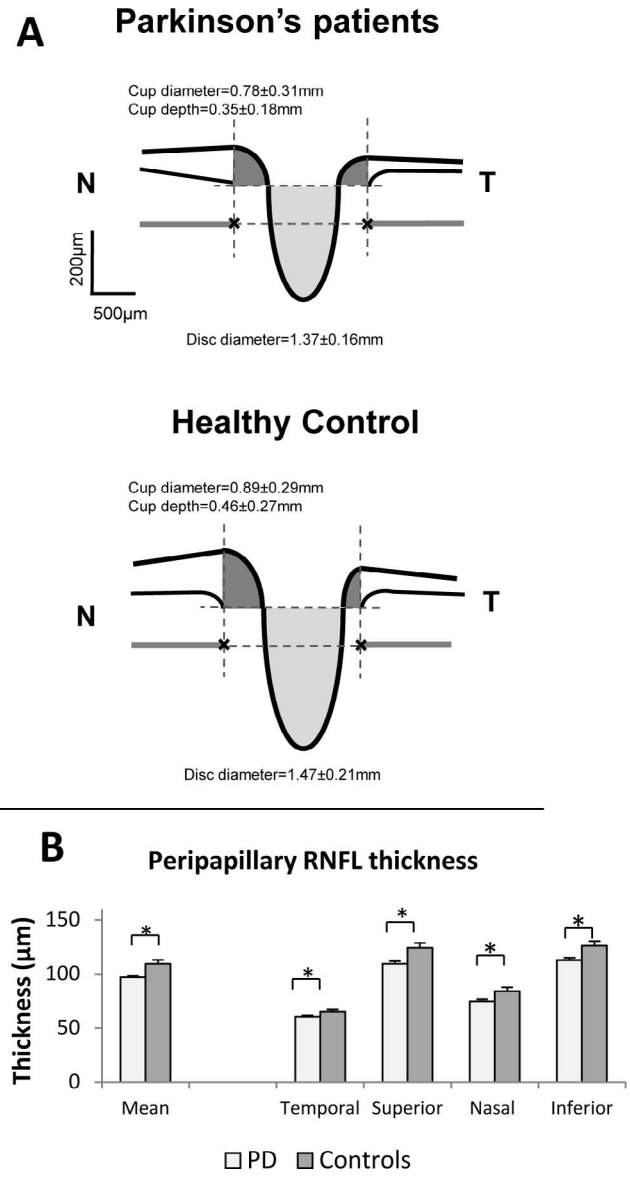

FIGURE 2. Cross-sectional schematic diagrams representing mean values of ONH parameters (mean ± SE) of patients with PD and controls (**A**) and average thickness of the peripapillary RNFL in participants with PD as compared with healthy controls in different quadrants (**B**). (**A**) *Upper horizontal dotted lines* represent horizontal offset (150 µm) used to determine cup diameters and the *lower horizontal dotted lines* indicate disc horizontal diameters. The *vertical dotted lines* show margins of rim areas. T is temporal and N is nasal. (**B**) *Error bars*: SD. *Significant difference between groups, $P \leq 0.05$.

However, statistical analysis showed significantly smaller cup depth and horizontal disc diameter in PD patients. No significant difference in cup diameter, area, cup/disc ratio, and rim parameters was found as compared with healthy controls (Fig. 2A; Supplementary Table S2).

Peripapillary RNFL was significantly thinner in the PD group, as compared with controls, for both the mean measurement and all measured segments (Supplementary Table S2; Fig. 2B).

Foveal Morphology

Visual inspection of the macular scans shows thinner retina with foveal "flattening" and pit decrease in PD more noticeable with longer duration of disease (Fig. 3).

Statistical analysis of foveal pit parameters showed increased width of the pit in PD, whereas the pit area and depth were not significantly different between PD patients and controls (Supplementary Table S3).

Semiautomated analysis of total retinal thickness and RNFL thickness showed overall retinal thinning in patients with PD, associated with simultaneous RNFL thinning in the inner annulus ($P = 0.02$, $P = 0.035$, $P = 0.05$, and $P = 0.04$ for the central, superior, nasal, and inferior quadrants, respectively; Fig. 4A).

Segmentation layers analysis (Fig. 4B; Supplementary Table S4) showed significant decrease in thicknesses of the RNFL in PD, mainly in the temporal and central areas.

Difference in the nasal GCL thickness was close to significant, being thicker in healthy controls. The ONL was significantly thinner in all analyzed areas in the PD group with statistically thicker OPL in the central zone as compared with healthy controls. Retinal pigment epithelial was statistically thinner in the PD group in the nasal area.

The difference in macular and ON parameters was larger between hemiretinae corresponding to the predominantly affected cerebral hemisphere and corresponding areas of healthy controls (Supplementary Table S5; Fig. 5) than for those of the less severely affected cerebral hemisphere. Differences in retinal thickness, ppRNFL thickness, retinal RNFL, ONL, and RPE parameters were mainly significant in the nasal segments of the hemiretinae corresponding to the predominantly affected cerebral hemisphere.

We did not identify any significant difference between the right and left eyes of participants or between ppRNFL of the hemiretinae corresponding to more and less severely affected cerebral hemisphere when compared directly with each other.

Correlation of OCT Parameters With Clinical Parameters

A positive significant correlation between the maximal horizontal and vertical cup diameters and a negative correlation of ppRNFL thickness in the peripapillary area and the HY was found.

Pit parameters were negatively correlated with duration of disease and central retinal thickness with duration of disease and HY. Inner segment and RPE thickness were negatively correlated with duration of disease, whereas INL was positively correlated with duration of disease. Visual acuity was positively correlated with GCL thickness (Supplementary Table S6).

The pit area and pit width were negatively correlated with the duration of disease. Peripapillary RNFL was negatively correlated with HY. Retinal thickness showed significant thinning with the duration of the disease and higher HY in the central area. Retinal nerve fiber layer thinning in the central zone correlated with HY. Longer duration of disease correlated significantly negatively with IS thickness in central area; RPE thickness in the nasal area and positively correlated with INL thickness. Visual acuity was positively correlated with GCL thickness (Supplementary Table S6).

DISCUSSION

In this study, investigating ON and macular morphology in PD patients, we found significant changes of the ON structure and individual retinal layers. Changes correlated to clinical parameters. We also found that the hemiretinae corresponding to the predominantly affected cerebral hemisphere were more affected.

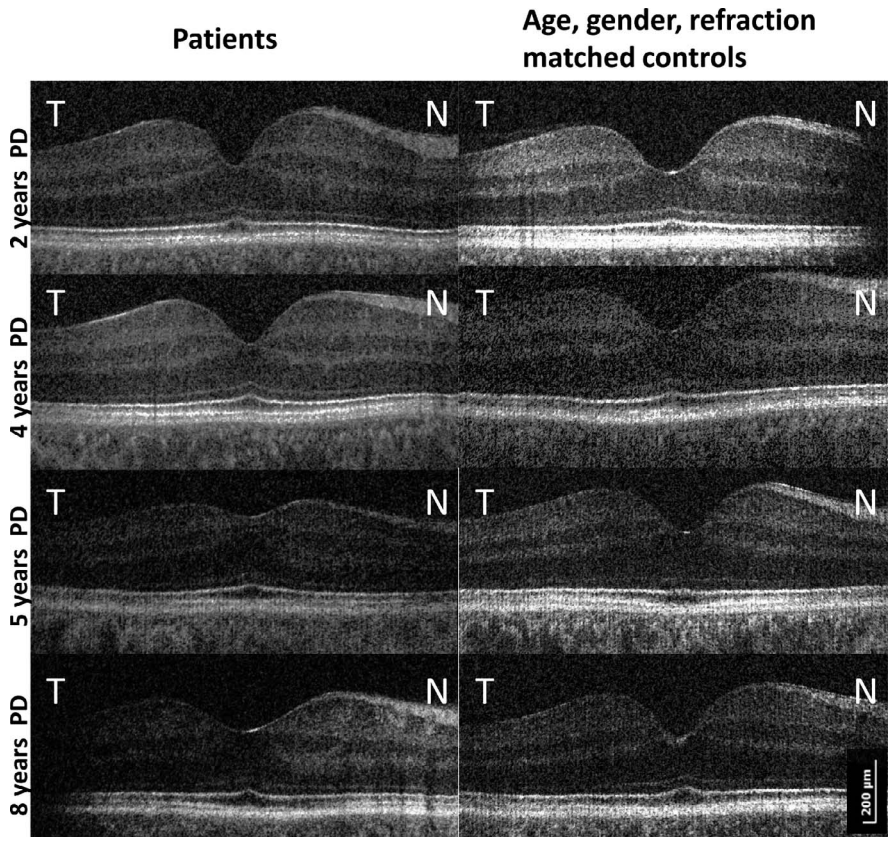

FIGURE 3. Horizontal SD-OCT b-scan images of the patients with 2-, 4-, 5-, and 8-years duration of PD, and healthy controls. Patients with PD have pit enlargement and flattening of the retina more apparent with increased duration of PD. In the patient with 5-years PD duration continuation of the OPL is clearly seen in the central fovea. T is temporal and N is nasal.

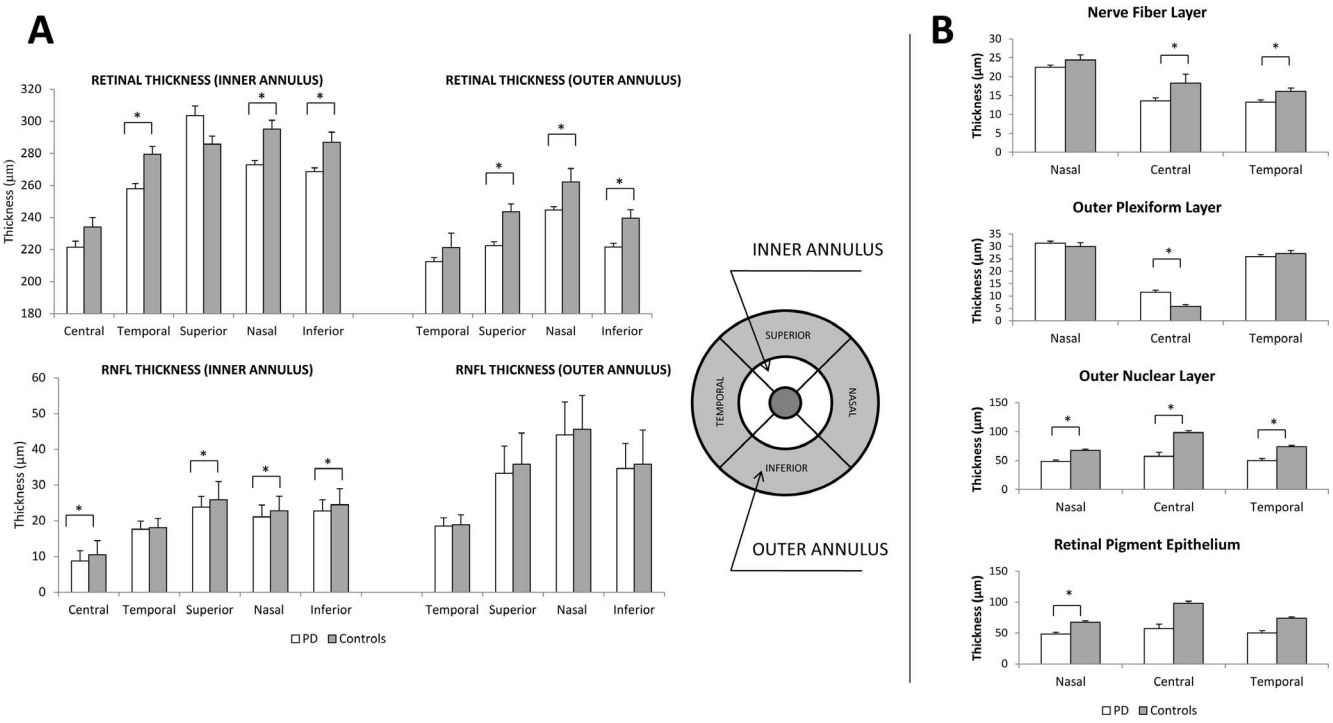

FIGURE 4. Average retinal and RNFL (µm) in PD (*white bars*) as compared with healthy controls (*gray bars*, [**A**], the diagram of the annuli is shown for the left eye) and thickness of selective individual retinal layers with significant difference in PD as compared with healthy controls (**B**). *Significant difference between groups, $P \leq 0.05$.

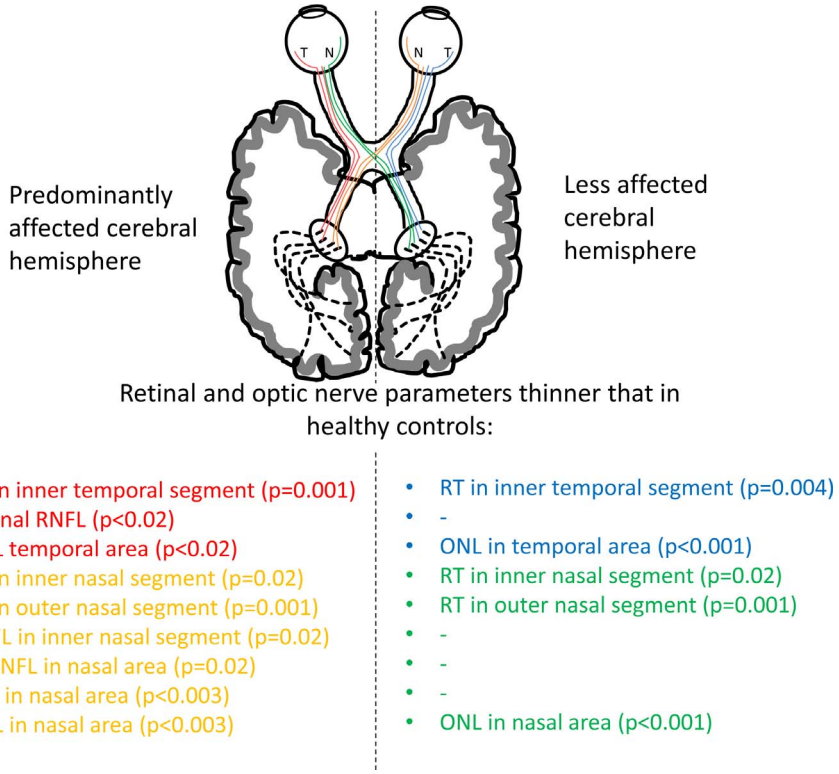

Figure 5. Schematic diagram of significant changes of the hemiretina corresponding to the more and less severely affected cerebral hemisphere as compared with controls. Hemiretinae corresponding to predominantly affected cerebral hemisphere are the contralateral nasal hemiretina (to the predominantly affected hemisphere, *orange*) and the ipsilateral temporal hemiretina (to the predominantly affected cerebral hemisphere, *red*). Hemiretinae corresponding to less affected cerebral hemisphere are the contralateral nasal hemiretina (to the less affected hemisphere, *green*) and the ipsilateral temporal hemiretina (to the less severely affected hemisphere, *blue*). RT, retinal thickness.

Optic Nerve Head Morphology

Although glaucoma has been reported to be more common in PD,[24] the ONH has not been analyzed using OCT previously. Axonal loss in patients with glaucoma is associated with severe RNFL thinning, rim reduction, and cup enlargement.[25] The majority of OCT studies in PD report significant reductions in peripapillary and macular RNFL.[16,26] None of our patients had elevated IOP. We also found in our PD patients severe ppRNFL thinning. However, in contrast with changes in glaucoma, in PD the ppRNFL thinning was not associated with rim reduction, cup enlargement, and increase in cup/disc ratio. Moreover, PD patients had a significantly shallower cup depth ($P = 0.03$). In glaucoma, even if advanced, superior and inferior quadrants retain typically thicker ppRNFL than nasal and temporal quadrants.[27] In contrast, in our study, PD patients had symmetrical ppRNFL loss in all quadrants. In addition, we found a significant decrease in the horizontal disc diameter in the PD group. Therefore, characteristics of ON changes in PD are different from glaucomatous changes of the ON. Consequently, visual field changes described in previous studies in PD,[5,28] and ON changes found in our study using OCT, are likely to be caused by a primary neurodegenerative process of the ON associated with PD rather than by glaucoma and/or raised IOP. We assume that significantly smaller cup depth and horizontal disc diameters in PD patients could also reflect neurodegenerative processes.

Foveal Morphology

Automated retinal and RNFL thickness analysis in the macular area confirmed previous findings of general reduction in retinal thickness associated with RNFL thinning both in the peripapillary and in the macular area.[6,19]

Literature regarding individual retinal layer changes in PD is controversial. It is not clear whether automated or manual retinal layer segmentation analysis is superior.

In an OCT study using automated retinal segmentation, Garcia-Martin et al.[15] described thinning of GCL, IPL, and INL thickening. However, this study is controversial as the thickness parameters of the analyzed retinal layers were not within the values reported in other studies using similar algorithms. Moreover, automated analysis showed increasing thickness for consecutive layers, corresponding to the anatomic position of the layer from RPE, but not to the actual thicknesses of the individual layer and it is likely that errors in layer recognition occurred.[20]

Aaker et al.,[29] using manual adjustment of automated segmentation (thickness of RNFL, GCL, IPL, INL), have not found any significant inner retinal layers thinning in patients with PD. By contrast, Roth et al.[30] and Muller et al.[31] described retinal inner layer thinning as well as thinning of outer retinal layers (ONL+RPE measured together and IS+OS+ RPE layers measured together) in PD.

Previously, RNFL and GCL thinning with reduction of the volume of the pit were described in Alzheimer's disease and patients with mild cognitive impairment.[32] Retinal nerve fiber layer and retinal thinning with GCL loss were also described in other neurological disorders including multiple sclerosis and schizophrenia.[33–35] Our results confirm earlier findings of thinning of the RNFL and GCL in the PD group that were also typical for other neurological disorders.

Shrier et al.[22] investigated retinal thickness at different distances from the center of the fovea and found significant intraocular asymmetry in PD group and suspected that changes of the "foveal slope architecture" together with GCL thickness could be a PD biomarker.

We also found a significant decrease in the width of the foveal pit. It was associated with OPL thickening. We assume that foveal remodelling in PD involves not only retinal thinning described by Shrier et al.[22] but also structural changes in retina.

In our study, we also found thinning of the RPE layer that, to our knowledge, has not previously been described. This layer is of particular interest as it has a high content of dopaminergic cells.[36] Retinal pigment epithelial thinning is in agreement with the reduction of RPE function on testing electrooculography in PD patients.[11] Retinal pigment epithelial thinning has not been described in other neurological conditions to our knowledge. Several recent PD studies found changes in the outer retinal layers and RPE when measured together. Authors have suggested possible thinning of the RPE as all outer retina layers, measured together with the RPE, were thinner in PD.[30,37] Foveal remodelling and RPE thinning, therefore, appear to be specific for PD and could be an important biomarker of PD.

Differences of Hemiretinae Corresponding to More and Less Severely Affected Cerebral Hemisphere

Asymmetry between cerebral hemispheres in PD, indicating asymmetric neurodegeneration in the nigrostriatal complex and cortex in earlier stages of PD, has been shown using magnetic resonance imaging. Changes were more pronounced on the side contralateral to the more severely affected body side.[38,39] Previously intraocular asymmetry in the retinal thickness has been described in patients with PD by Shrier et al.[22] comparing the right and the left eyes.[22] However, the authors did not clarify which side was more affected. It is also noted that in this study refractive changes, coexistent ophthalmic pathology, and the fact that nasal axons cross in the chiasm were not taken into account while comparing the difference in severity in brain hemispheres.[22] Our study, using strict inclusion and exclusion criteria for patients and controls, did not identify any significant difference between the right and left eyes. We found that changes of the macula and ON parameters were more pronounced in the hemiretinae that was related to the predominantly affected cerebral hemisphere. These findings indicate that the retina is affected in a very similar way as the brain, with the retinal hemifields corresponding to the predominantly affected hemisphere being affected more severely as well. This observation underlines that the retina is related directly to brain changes and these described changes can serve as a biomarker for PD.

Correlation of OCT Parameters With Clinical Parameters

In agreement with previous findings, ppRNFL as well as retinal and macular RNFL thicknesses were negatively correlated with the duration of the disease and HY.[40]

Our data showed significant IS (central) and RPE (nasal) thinning with the duration of the disease. These results, therefore, reflect progressive changes in the outer retinal layers in PD group.

In our study, the pit area and width demonstrated a negative correlation with the duration of PD. However, we have not found any statistical difference between PD and healthy controls for the pit depth and area as compared with our age-matched control group. This could possibly be explained by normative data also showing central retinal thinning with age.[24] These studies mainly involve controls with the age range up to 60 to 68 years. Possibly "flattening" of the pit shape is associated to physiological age-related changes and also present in the healthy population. Therefore, a study with healthy controls over 70 years of age would be interesting to determine physiological aging of the retina.

In our study, all stages of PD may not be adequately represented as we were unable to examine patients with advanced disease due to reduced mobility.

Based on the macula and ON changes described in this research further studies are required to correlate selective retinal changes and electrodiagnostic parameters; possible parallels of the eye morphology and severity of the oculomotor changes.

The cohort of participants with PD included in this study were mostly moderate or late stage PD with an average score on the HY scale of 3.92 and disease duration of over 6 years. It would be interesting to analyze eye morphology in patients with newly diagnosed PD and define the retinal/ONH factors that could help with early diagnosis. In summary, we found ON changes including ppRNFL thinning in all quadrants and shallow cups with normal diameters indicating that ON changes in PD are likely to be caused by primary neurodegeneration and are different to ON changes described in glaucoma. Remodelling of the fovea with retinal thinning, pit widening, central OPL thickening, and RPE thinning was observed in PD. Changes of specific layers are different from those in other neurodegenerative diseases such as Alzheimer's disease. They were also more pronounced in advanced stages of PD, with longer disease duration and in the hemiretinae corresponding to the cerebral hemisphere with more severe neurodegenerative changes. Therefore, retinal changes have potential to be used as biomarkers for PD.

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