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# Visual dysfunction and its correlation with retinal changes in patients with Parkinson disease

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# Visual dysfunction and its correlation with retinal changes in patients with Parkinson disease.

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SUBTITLE: Visual acuity, contrast sensitivity vision and color vision are affected in Parkinson disease. Visual dysfunction in these patients correlates with structural changes in the retina measured with Spectral domain OCT.

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**Aim**: To evaluate visual dysfunction and its correlation with structural changes in the retina in patients with Parkinson disease (PD).

**Methods:** Patients with PD (n=37) and controls (n=37) underwent visual acuity (VA), color vision (using the Farnsworth and L'Anthony desaturated D15 color tests), and contrast sensitivity vision (CSV; using the Pelli Robson chart and CSV 1000E test) evaluation to measure visual dysfunction. Structural measurements of the retinal nerve fiber layer (RNFL), and macular and ganglion cell layer (GCL) thicknesses were obtained using spectral domain optical coherence tomography (SD-OCT). Comparison of obtained data and correlation analysis between functional and structural results were performed.

**Results:** VA (in all different contrast levels) and all CSV spatial frequencies were significantly worse in PD patients than in controls (P < 0.05). Color vision was significantly affected (p<0.05) based on the L'Anthony color test. Macular thinning was detected in the central, outer (inferior and temporal), and superior sectors (p<0.05), and the RNFL had significant thinning in the temporal quadrant (p<0.05). Significant GCL loss was observed in the superior and superonasal sectors and the GCL + minimum inner plexiform layer (p<0.05). CSV was the functional parameter most strongly correlated with structural measurements in PD. Color vision was associated with most GCL measurements. Macular thickness was strongly correlated with macular volume and functional parameters (r > 0.70, p<0.05).

**Conclusions:** Patients with PD had visual dysfunction that correlated with structural changes evaluated by SD-OCT. Macular and GCL measurements may be reliable indicators of visual impairment in PD patients.



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Strengths and limitations of this study:

The present study provides further information on visual dysfunction in Parkinson disease (PD) patients and corroborates previously published results on this subject. In our study the parameters corresponding to visual acuity (VA), color vision (CV) and contrast sensitivity vision (CSV) were altered in PD patients, and CSV correlated with most of the structural data. We detected significant reductions in the macular, the retinal nerve fiber layer (RNFL), and the ganglion cell layer (GCL) thicknesses. The GCL correlated most with the visual function parameters.

We consider the sample size to be the most important limitation of this study. The small number of patients may have affected the significance of our results compared to previous studies; however, we detected significant reductions in the macular, RNFL, and GCL thicknesses (consisting with previous published results).

The strengths of this study should be resumed by the following points:

- We detected alteration in VA (at different contrast levels), CSV and CV in PD patients.
  CSV correlated with most of the structural data.
- We detected significant reductions in the macular, RNFL, and GCL thicknesses. The GCL correlated most with the visual function parameters.
- There are only 2 other published articles evaluating the association between visual dysfunction and morphologic parameters. Results provided by these previous studies differ from our results, possibly due to different measurement methods and sample size.
- CV in our study was assessed by L'Anthony's and Farnsworth D15 color tests, which may provide more specific information about color deficiencies. These tests are not commonly used to evaluate color deficiencies in PD patients.

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Macular thickness and macular volume were strongly associated with functional
parameters. This is the first study demonstrating strong correlation between structural and
functional visual parameters in PD patients.
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# **Introduction**

Foveal vision alterations are associated with Parkinson disease (PD), and seem to be caused by dysfunction of the intraretinal dopaminergic circuitry and final retinal output to the brain.[1] Recent studies demonstrated retinal thinning in PD patients compared with healthy subjects.[2-5] Several studies report a correlation between functional disability and axonal loss observed in the optic nerve in multiple sclerosis, another neurodegenerative process.[6,7] PD patients are also reported to have decreased contrast sensitivity and color vision, and altered visual evoked potentials.[1,8-13] To our knowledge, however, very few studies have assessed visual dysfunction in PD and its correlation with morphologic parameters.[14,15]

In the present study, we evaluated visual acuity (VA) using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart, contrast sensitivity vision (CSV) using the CSV-1000E test and Pelli-Robson chart, and color vision using the Farnsworth and L'Anthony tests in PD patients and healthy controls to examine the association between visual dysfunction and morphologic parameters.

# Material and methods

Thirty-seven eyes of 37 patients with definite PD and 37 eyes of 37 age- and sex-matched healthy individuals were recruited for the study. The study was performed at Miguel Servet University Hospital in Zaragoza, Spain. All procedures adhered to the tenets of the Declaration of Helsinki, and all participants provided informed consent to participate in the study.

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The diagnosis of PD was based on standard clinical and neuroimaging criteria.[16] Information about disease severity was assessed using the Hoehn Yahr scale,[17] and disease duration and treatment were recorded. Exclusion criteria were the presence of significant refractive errors (>5 diopters of spherical equivalent refraction or 3 diopters of astigmatism); intraocular pressure  $\geq$ 21 mmHg; media opacifications; concomitant ocular diseases, including history of glaucoma or retinal pathology; and systemic conditions that could affect the visual system. The healthy controls had no history and no evidence of ocular or neurologic disease of any nature; their bestcorrected visual acuity (BCVA) was >20/30 based on the Snellen scale.

All subjects underwent a complete neuro-ophthalmic evaluation that included pupillary, anterior segment, and funduscopic examination. Visual function was assessed by evaluating BCVA using an ETDRS chart, CSV using the CVS-1000E test and Pelli-Robson chart, and color vision using the Farnsworth desaturated D15 and L'Anthony desaturated D15 tests. Structural analysis of the retina was performed using Spectral domain (SD) optical coherence tomography (OCT) with the Cirrus High definition (HD) OCT (Carl Zeiss Meditec Inc, Dublin, CA), which included three different protocols: macular protocol (for macular thickness analysis), RNFL protocol, and ganglion cell protocol (for individual analysis of this layer).

LogMAR visual acuity (VA) was evaluated at three different contrast levels: 100% (HCVA, using ETDRS chart), 2.50%, and 1.25% (LCVA, using Low-Contrast Sloan Letter Charts - Precision Vision, LaSalle, IL-), The percentage indicating the level of contrast, i.e., 100% representing black letters over white background and 1.25% light grey letters over white background. All measurements were obtained under monocular vision and controlled lighting conditions with best correction.

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Contrast sensitivity provides more complete information about visual function than visual acuity tests. CSV was evaluated in our patients using the Pelli-Robson chart and the CVS-1000E test. The Pelli-Robson chart comprises horizontal lines of capital letters organized into groups of three (triplets) with two triplets per line. Within each triplet, all letters have the same contrast. The contrast decreases from one triplet to the next, even within each line. All patients were evaluated under both monocular and binocular vision at a distance of 1 meter from the chart and under controlled fotopic conditions (85 cd/m<sup>2</sup>). The score corresponding to the last triplet of letters seen by the patient was recorded.

The CSV-1000E instrument is used worldwide for standardized CSV and glare testing. All patients were evaluated at a distance of 2.5 meters from the chart under monocular vision at 4 different spatial frequencies (3, 6, 12, and 18 cycles per degree [cpd]). The chart comprises four rows with 17 circular patches each. The patches present a grating that decreases in contrast moving from left to right across the row. The patient indicates whether the grating appears in the top patch or the bottom patch for each column. Each contrast value for each spatial frequency was transformed into a logarithmic scale according to standardized values.

Color vision was assessed using the Color Vision Recorder (CVR) program. CVR software analyzes chromatic discrimination by classification of colors. The program includes the classic test of Farnsworth 100-hue (FM-100), Farnsworth - Munsell D15, and L'Anthony D15. All patients in the study were evaluated using the Farnsworth - Munsell D15 and L'Anthony D15 protocols and different output parameters such as the Confusion Index (C-index), the Color Confusion Index (CCI), the Confusion angle (Conf Ang), and the Scatter Index (S-index) were recorded.<sup>18,19</sup> The tests were performed under monocular vision. Page 9 of 26

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Structural measurements of the retina were obtained using the Cirrus OCT device. The same experienced operator performed all scans and did not apply manual correction to the OCT output. We used an internal fixation target because it provides the highest reproducibility and rejected poor quality scans prior to data analysis. The Cirrus OCT macular cube 512 x 128 protocol provides a macular volume measure and retinal thickness values for nine areas. These areas include a central 1-mm circle representing the fovea, and inner and outer rings measuring 3 mm and 6 mm in diameter, respectively. The inner and outer rings are divided into four quadrants each. The Cirrus OCT optic disc protocol generates images with 200 linear scans enabling analysis of the RNFL of a 6-mm<sup>3</sup> area around the optic nerve. For each scan series of RNFL measurements, we assessed the mean, superior, inferior, temporal, and nasal thickness. Cirrus segmentation analysis for retinal layers also provides measurements of the GCL thickness, evaluating six areas of the macular cube (superior, superonasal, inferior, inferotemporal, and superotemporal sectors) and measurements of the mean and minimum GCL plus the inner plexiform layer (GCL + IPL) value of a set of 360 spokes, where each average represents the mean number of the pixels along that spoke that lies within the measurement annulus. The minimum is selected because the thinnest portion of the GCL + IPL in the perifoveal region is considered to indicate damage to the ganglion cells.

All data analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL). Due to the parametric distribution of the data, differences between evaluations of PD patients and healthy subjects were compared using Student's t-test. The linear correlation between structural and functional parameters was determined using Pearson's correlation coefficient. Values of p < 0.05 were considered to indicate statistical significance. Each eye was considered separately, and one eye from each patient was randomly selected for analysis.

# **Results**

Thirty-seven patients with PD and 37 healthy controls were included in the study. The mean age of the patients with PD was 69 years (range: 58–74 years) and the mean age of the healthy controls was 68 years (range: 60–76 years). Age (p=0.361), sex (p=0.441), and intraocular pressure (p=0.720) did not differ significantly between healthy controls and patients with PD. Mean time from diagnosis of PD was 13.2 years and the median Hoehn Yahr stage was 2.7.

# Functional parameters

PD patients had a lower BCVA at all three contrast levels of the ETDRS chart compared to the controls ( $0.18\pm0.26$  in patients vs  $-0.065\pm0.9$  in controls at 100%, p=0.001;  $0.59\pm0.21$  vs  $0.44\pm0.13$  at 2.50%, p=0.01; and  $0.61\pm0.23$  vs  $0.58\pm0.16$  at 1.25%, p=0.009). CSV was affected in patients at all four spatial frequencies of the CSV 1000E chart (3, 6, 12, and 18 cpd) when analyzed based on the number of correct localized gratings (p=0.001, <0.001, <0.001, and 0.004 respectively). The Pelli Robson results also revealed a significant reduction in CSV in PD patients (1.71 in patients vs 1.89 in controls, p=0.02). Color vision (L'Anthony test indexes) was also affected in PD. The results are shown in Table 1.

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	HEALTHY CO	ONTROLS	PARKINSON DISEASE PATIENTS		SIGNIFICANCE	
	Mean	SD	Mean	SD	( <b>P</b> )	
VA ETDRS 100	-0.06	0.096	0.18	0.26	0.001	
VA ETDRS 2.5	0.44	0.13	0.59	0.22	0.010	
VA ETDRS 1.25	0.58	0.16	0.62	0.23	0.009	
Pelli Robson	1.89	0.11	1.71	0.17	0.002	
CSV 1000 3 cpd	1.72	0.16	1.49	0.35	0.001	
CSV 1000 6 cpd	1.94	0.13	1.62	0.34	0.000	
CSV 1000 12 cpd	1.62	0.17	1.26	0.41	0.000	
CSV 1000 18 cpd	1.11	0.22	0.73	0.34	0.004	
Farnsworth AC CCI	1.11	0.22	0.73	0.34	0.851	
Farnsworth C- index	1.10	0.20	1.24	0.42	0.093	
Farnsworth CCI	1.07	0.12	1.14	0.24	0.110	
Farnsworth Conf Angle	63.90	11.15	65.84	7.49	0.392	
Farnsworth S-index	1.56	0.22	1.64	0.39	0.278	
Farnsworth time	78.67	28.96	82.91	33.10	0.616	
L'Anthony AC CCI	1.05	0.19	1.02	0.18	0.489	
L´Anthony C-index	1.43	0.39	1.64	0.53	0.058	
L´Anthony CCI	1.30	0.23	1.44	0.37	0.066	
L´ Anthony Conf Angle	62.31	14.74	71.91	9.25	0.002	
L´Anthony S-index	1.69	0.43	1.95	0.48	0.020	
L´ Anthony time	77 14	25.99	84 09	39 31	0.431	

Structural parameters

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OCT measurements indicated significant differences in superior macular sectors, in the outer inferior, outer temporal, and central macular thickness (results are shown in Table 2, Figure 1). The segmentation analysis revealed a significantly reduced GCL in PD patients in the superior  $(81.64\pm7.08 \ \mu\text{m} \text{ in patients vs } 84.55\pm4.32 \ \mu\text{m} \text{ in controls; p=0.032})$  and superonasal sectors  $(81.04\pm7.23 \ \mu\text{m} \text{ vs } 85.28\pm4.78 \ \mu\text{m}; \text{p=0.029})$ . The minimum GCL+IPL value was also reduced  $(80.18\pm6.19 \ \mu\text{m} \text{ vs } 82.45\pm3.60 \ \mu\text{m}; \text{p=0.005})$ . The RNFL was significantly reduced in the temporal quadrant in PD patients (Table 2, Figure 1).

	CONT	ROLS	PARKI DISE	NSON ASE	
Structural parameters	Mean	SD	Mean	SD	Р
Macular measurements					
Central macular thickness	254.75	17.903	248.96	17.765	0.028
Inner superior macular thickness	327.34	13.094	▲ 325.73	19.329	0.019
Inner nasal macular thickness	328.52	13.263	325.45	17.098	0.091
Inner inferior macular thickness	326.14	13.179	324.82	17.921	0.106
Inner temporal macular thickness	315.90	13.615	312.82	15.760	0.945
Outer superior macular thickness	284.76	9.418	279.44	17.981	0.008
Outer nasal macular thickness	302.41	12.167	299.18	17.064	0.074
Outer inferior macular thickness	277.79	10.755	273.76	16.798	0.045
Outer temporal macular thickness	271.52	10.992	266.23	18.987	0.013
Ganglion cell layer thickness					
Superior	84.55	4.323	81.61	7.087	0.032
Superonasal	85.28	4.780	81.04	7.234	0.029
Inferonasal	84.66	5.314	81.82	7.521	0.135
Inferior	84.34	5.052	81.91	6.252	0.389
Inferotemporal	85.79	4.003	83.73	4.860	0.233
Temporal	83.76	3.324	82.27	5.312	0.069
Average IPL+GCL	84.83	4.071	82.73	6.230	0.095
Min IPL+ GCL	82.45	3.601	80.18	6.194	0.005
RNFL thickness					
Average	96.17	6.714	94.88	11.505	0.105
Superior	117.90	10.965	118.68	16.861	0.115
Nasal	73.59	12.724	72.40	15.182	0.345

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Inferior	128.14	14.060	123.20	22.907	0.075
Temporal	64.97	8.218	61.48	10.553	0.027

# Correlation between functional and structural parameters

CSV was the functional parameter most frequently associated with structural measurements in PD. The Pelli Robson CSV results correlated with GCL thickness in all sectors, although the association was not strong (r < 0.5). The superonasal (r=0.40, p=0.010), inferonasal (r=0.40, p=0.010, inferior (r=0.43, p=0.005), superotemporal sector (r=0.43, p=0.006), and mean GCL+IPL (r=0.45, p=0.004) values had the highest correlations. The Pelli Robson results also correlated with the thickness in different sectors of the RNFL (mean, superior, and inferior sectors). Measurements with the CSV 1000E at different spatial frequencies correlated significantly with most GCL measurements. The superonasal (r=0.40, p=0.013) and superotemporal (r= 0.44, p= 0.006) thickness, mean GCL +IPL thickness (r= 0.40, p= 0.012), and the minimum GCL + IPL (r= 0.40, p=0.011) at a spatial frequency of 6 cpd; and the superotemporal (r= 0.41, p= 0.01) thickness and the minimum GCL + IPL thickness (r= 0.43, p=0.006) at a spatial frequency of 18 cpd had the strongest correlations between CSV 1000E and GCL thickness. Spatial frequencies of 6 cpd and 18 cpd were strongly correlated with mean macular thickness (r= 0.79, p= 0.012; r= 0.77, p= 0.016, respectively) and macular volume (r= 0.78, p= 0.013; r= 0.78, p= 0.014, respectively).

Color vision assessed by the L'Anthony test was also associated with the structural parameters: both the L'Anthony CCI and C-index values were significantly correlated with most of the GCL measurements (see Table 3). A significant association between color vision and the RNFL parameters was only found in isolated sectors. All outer macular parameters were significantly correlated with the L'Anthony CCI and C-index results (see Table 3).

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			L'Anthony's	s color test		
	C-index	р	CCI	р	S-index	р
Macular thickness						
Central	-0.019	0.905	-0.059	0.716	-0.017	0.915
Inner superior	-0.146	0.369	-0.119	0.463	-0.167	0.302
Inner nasal	-0.055	0.735	-0.044	0.788	-0.040	0.807
Inner inferior	-0.073	0.654	-0.064	0.697	-0.074	0.649
Inner temporal	-0.049	0.764	-0.031	0.850	-0.126	0.439
Outer superior	-0.377	0.017	-0.380	0.015	-0.271	0.090
Outer nasal	-0.341	0.031	-0.323	0.042	-0.310	0.051
Outer inferior	-0.360	0.022	-0.353	0.025	-0.375	0.017

The strongest correlation was between the mean macular thickness and macular volume and the L'Anthony CCI, C-index, and S-index results. No significant correlations were found between the Farnsworth's test parameters and structural measurements.

Outer temporal	-0.360	0.023	-0.361	0.022	-0.350	0.027
Macular average	-0.691	0.019	-0.657	0.028	-0.709	0.015
Macular volume	-0.686	0.020	-0.647	0.032	-0.709	0.015
Ganglion cell layer thickness						
Superior	-0.380	0.015	-0.369	0.019	-0.287	0.072
Superonasal	-0.383	0.015	-0.337	0.033	-0.350	0.027
Inferonasal	-0.338	0.033	-0.313	0.049	-0.268	0.094
Inferior	-0.341	0.031	-0.311	0.051	-0.282	0.078
Inferotemporal	-0.252	0.116	-0.263	0.101	-0.203	0.208
Temporal	-0.403	0.010	-0.437	0.005	-0.314	0.048
Average IPL+ GCL	-0.381	0.015	-0.358	0.023	-0.319	0.045
Minimun IPL+ GCL	-0.338	0.033	-0.326	0.040	-0.290	0.069

The VA ETDRS results correlated strongly with mean macular thickness and macular volume (see Table 4). There were significant but mild associations between the GCL parameters and VA at 100% (superonasal, inferonasal, and mean GCL + IPL thickness, r=-0.38, p=0.016; r=-0.35, p=0.016; and r=0.35, p=0.029, respectively) and 2.50% (superonasal sector, r=-0.36, p=0.023).

	Macular thickness	P value	Macular volumen	P value
VA ETDRS 100	-0.765	0.006	-0.761	0.007
VA ETDRS 1.25	-0.718	0.013	-0.715	0.013
VA ETDRS 2.50	-0.738	0.010	-0.729	0.011

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# **Discussion**

In the present study, we evaluated the visual function parameters and assessed the association between visual dysfunction and morphologic changes in the retina of 37 patients with PD. Parameters corresponding to VA at different contrast levels, and all CSV tests results were altered in PD patients in comparison with healthy subjects. Moreover, contrast sensitivity was the most affected parameter in our study and correlated with most of the structural data. Color vision was measured with two different tests, the Farnsworth and L'Anthony 15 D tests. These tests provide information for differentiating subjects with severe loss of color vision from those with milder color defects or normal color vision, and also can be used to evaluate acquired loss of color vision. In our study, only the L'Anthony test results were significantly altered in PD patients.

Previous studies have indicated that PD patients lose foveal contrast sensitivity to patterns to which normal observers are most sensitive (i.e., requiring the least contrast for detection).[8,9] Ganglion cells in the retina show adaptation to visual contrast and pool visual inputs over their receptive fields through an array of parallel bipolar cells with smaller receptive fields.[20] In the mammalian retina, color vision and contrast sensitivity are modulated through D1 and D2 receptors. These dopaminergic receptors are differentially located in the retinal layers and a complete lack of activation leads to signal dispersion and alterations in color vision and contrast sensitivity.[2]

Alteration of the retinal layers in PD was first demonstrated in 2004.[21] Since then, various studies have demonstrated different results.[3-5,21,22] A previous study carried out by our team suggested that macular thickness and the inner retinal layers were affected in PD patients.[23]

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GCL thickness was inversely correlated with disease duration and PD severity, and predictive of axonal damage in these patients.[25] The present study included a smaller number of patients, which may have affected the significance of our results compared to previous studies. Despite the small number of subjects in the present study, however, we detected significant reductions in the macular, RNFL, and GCL thicknesses. The GCL correlated most with the visual function parameters: GCL thickness was directly associated with VA and CSV measured at all different spatial frequencies, and inversely correlated with the color vision indexes. Thus, GCL thinning is linked to color deficiencies, contrast sensitivity loss, and lower vision at different contrast levels in PD patients.

The degree of correlation is usually classified as low (<0.30), moderate (0.30–0.70), or strong (>0.70). Our results revealed a low and moderate degree of correlation between most parameters, consistent with findings in other neurodegenerative diseases.[24] Macular thickness and macular volume, however, were strongly associated with functional parameters (VA, CS, and L'Anthony CCI, C-index, and S-index). This strong association, to the best of our knowledge, has not been previously demonstrated in PD.

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There are very few studies of the correlation between functional and structural parameters in PD patients. Adam et al [14] demonstrated a significant reduction in the inner retinal layer complex (RNFL + GCL + IPL) in PD patients, but no association with contrast sensitivity (measured with the Pelli Robson chart). A very recent study by Kaur et al [15] demonstrated a correlation between functional parameters and GCL thinning, consistent with our results. Kaur et al, however, found no significant alterations in VA or color vision in PD patients and the severity of the disease was not correlated with structural parameters, in contrast to other studies that demonstrate an association between macular and GCL thickness and disease duration and

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severity.[23,25] Although the severity of the disease in our sample (based on the Hoehn Yahr scale) was similar to that in Kaur's study, the duration of the disease in our study was higher than that in Kaur's patients (13 years vs 5 years), which may account for some of the differences in the results between the two studies. These discrepancies (and similarities) support the need for more studies on this topic. Our results, together with previously published studies,[15,24] suggest that the GCL could be a reliable indicator of structural alterations in the retina of PD patients, demonstrating a significant correlation with functional tests in these patients. The results of the present study have important implications for clinical diagnosis and functional deficits in patients with PD, and highlight the importance of visual function tests in the evaluation of these patients.

In conclusion, visual dysfunction was significantly correlated with morphologic parameters in PD patients. PD patients present with a reduction in macular, RNFL, and GCL thickness, with changes in the GCL being most closely associated with visual dysfunction.

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V. Polo: Research project: organization. Statistical analysis and Manuscript: Review and critique.

M. Satue: Research project: Conception, design, organization and execution. Statistical analysis:

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# Legends

Figure 1: Structural parameter means of macular, ganglion cell and retinal nerve fiber layer thickness obtained with Cirrus HD coherence tomography device, comparing healthy controls and patients with Parkinson's disease. HD, high definition; GCL, ganglion cell layer; IPL, inner plexiform layer; RNFL, retinal nerve fiber layer.

Table 1: Mean and standard deviation (SD) of visual functional parameters in healthy controls and subjects with Parkinson disease. Results in bold letters indicate statistical significance (p<0.05). Abbreviations: VA, visual acuity; ETDRS, early treatment diabetic retinopathy study; cpd, cicles per degree; AC CCI, age corrected color confusion index; CCI, color confusion index; C-index, confusion index; Conf Angle, confusion angle; S-index, scatter index; PD, Parkinson disease.

Table 2: Mean and standard deviation (SD) of structural parameters (retinal nerve fiber layer, ganglion cell layer and macular thicknesses) obtained with the Cirrus HD optical coherence tomography device in healthy controls and subjects with Parkinson disease. Bold letters indicate statistical significance (p<0.05). Abbreviations: IPL, inner plexiform layer; GCL, ganglion cell layer; RNFL, retinal nerve fiber layer; HD, high definition.

Table 3: Correlation between macular and ganglion cell layer structural measurements and color vision evaluated with L'Anthony's color test in patients with Parkinson disease. Data in bold type correspond to statistically significant correlations (p value <0.05). Abbreviations: GCL,

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ganglion cell layer; IPL, inner plexiform layer; C-index, Confusion index; CCI, color confusion index; S-index, Scatter index.

Table 4: Correlation between visual acuity measured with ETDRS chart at different levels of contrast (in %) and macular structural measurements (thickness and volume) in patients with Parkinson disease. Correlation data in bold type are statistically significant (p value <0.05). lacuny, Abbreviations: VA, visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

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# Visual dysfunction and its correlation with retinal changes in patients with Parkinson disease

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4 5	1	visual dysiunction and its correlation with retinal changes in patients
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50 51	21	Hospital and based on the principles of the Declaration of Helsinki.
52	22	This research received no specific grant from any funding agency in the public, commercial or
53 54	23	not-for-profit sectors.
55 56	24	The authors disclose no conflict of interest.
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SUBTITLE: Visual acuity, contrast sensitivity vision and color vision are affected in Parkinson disease. Visual dysfunction in these patients correlates with structural changes in the retina

- measured with Spectral domain OCT.

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1 2		
2 3 4	32	Abstract
5 6 7 8 9 10 11 12 13 14 15 16 17	33	Objectives: To evaluate visual dysfunction and its correlation with structural changes in the
	34	retina in patients with Parkinson disease (PD).
	35	Methods: Patients with PD (n=37) and controls (n=37) were included in a observational cross-
	36	sectional study and underwent visual acuity (VA), color vision (using the Farnsworth and
	37	L'Anthony desaturated D15 color tests), and contrast sensitivity vision (CSV; using the Pelli
	38	Robson chart and CSV 1000E test) evaluation to measure visual dysfunction. Structural
	39	measurements of the retinal nerve fiber layer (RNFL), and macular and ganglion cell layer
18	40	(GCL) thicknesses were obtained using spectral domain optical coherence tomography (SD-
19 20	41	OCT). Comparison of obtained data and correlation analysis between functional and structural
21 22 23 24 25 26 27 28 29 30 31 32 33	42	results were performed.
	43	Results: VA (in all different contrast levels) and all CSV spatial frequencies were significantly
	44	worse in PD patients than in controls ( $P < 0.05$ ). Color vision was significantly affected
	45	(p<0.05) based on the L'Anthony color test. Macular thinning was detected in the central, outer
	46	(inferior and temporal), and superior (inner and outer) sectors (p<0.05), and the RNFL had
	47	significant thinning in the temporal quadrant (p<0.05). Significant GCL loss was observed in the
	48	superior and superonasal sectors and the minimum GCL + inner plexiform layer (p< $0.05$ ). CSV
34	49	was the functional parameter most strongly correlated with structural measurements in PD.
35 36	50	Color vision was associated with most GCL measurements. Macular thickness was strongly
37 38	51	correlated with macular volume and functional parameters (r >0.70, p<0.05).
39 40	52	Conclusions: Patients with PD had visual dysfunction that correlated with structural changes
41	53	evaluated by SD-OCT. Macular and GCL measurements may be reliable indicators of visual
42	54	impairment in PD patients.
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- 3 4	57	Strengths and limitations of this study:
5 6	58	
7 8 9	59	The strengths of this study should be resumed by the following bullet points:
10 11 12	60	- We detected alteration in VA (at different contrast levels), CSV and CV in PD patients.
13 14	61	CSV correlated with most of the structural data.
15 16 17	62	- We detected significant reductions in the macular, RNFL, and GCL thicknesses. The
18 19	63	GCL correlated most with the visual function parameters.
20 21	64	- There are only 2 other published articles evaluating the association between visual
22 23 24	65	dysfunction and morphologic parameters. Results provided by these previous studies
25 26	66	differ from our results, possibly due to different measurement methods and sample size.
27 28	67	- CV in our study was assessed by L'Anthony and Farnsworth D15 color tests, which may
29 30 31	68	provide more specific information about color deficiencies. These tests are not commonly
32 33	69	used to evaluate color deficiencies in PD patients.
34 35	70	- Macular thickness and macular volume were strongly associated with functional
36 37 38	71	parameters. This is the first time such a strong correlation is reported (r>0.70).
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72	Introduction
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74	Foveal vision alterations are associated with Parkinson disease (PD), and seem to be caused by
75	dysfunction of the intraretinal dopaminergic circuitry and final retinal output to the brain.[1]
76	Recent studies demonstrated retinal thinning in PD patients compared with healthy subjects.[2-5]
77	Several studies report a correlation between functional disability and axonal loss observed in the
78	optic nerve in multiple sclerosis, another neurodegenerative process.[6,7] PD patients are also
79	reported to have decreased contrast sensitivity and color vision, and altered visual evoked
80	potentials.[1,8-13] To our knowledge, however, very few studies have assessed visual
81	dysfunction in PD and its correlation with morphologic parameters.[14,15]
82	In the present study, we evaluated visual acuity (VA) using an Early Treatment Diabetic
83	Retinopathy Study (ETDRS) chart, contrast sensitivity vision (CSV) using the CSV-1000E test
84	and Pelli-Robson chart, and color vision using the Farnsworth and L'Anthony tests in PD
85	patients and healthy controls to examine the association between visual dysfunction and
86	morphologic parameters.
87	
88	Material and methods
89	Thirty-seven eyes of 37 patients with definite PD and 37 eyes of 37 age- and sex-matched
90	healthy individuals were recruited for the study. The study was performed at Miguel Servet
91	University Hospital in Zaragoza, Spain. All procedures adhered to the tenets of the Declaration
92	of Helsinki, and all participants provided informed consent to participate in the study.

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The diagnosis of PD was based on standard clinical and neuroimaging criteria.[16] Information about disease severity was assessed using the Hoehn Yahr scale [17] and the Unified Parkinson Disease Rating Scale III (UPDRS) [18]. Disease duration and treatment were recorded. Exclusion criteria were the presence of significant refractive errors (>5 diopters of spherical equivalent refraction or 3 diopters of astigmatism); intraocular pressure >21 mmHg; media opacifications; concomitant ocular diseases, including history of glaucoma or retinal pathology; and systemic conditions that could affect the visual system. The healthy controls had no history and no evidence of ocular or neurologic disease of any nature; their best-corrected visual acuity (BCVA) was  $\geq 20/30$  based on the Snellen scale.

All subjects underwent a complete neuro-ophthalmic evaluation that included pupillary, anterior segment, and funduscopic examination. Visual function was assessed by evaluating BCVA using an ETDRS chart, CSV using the CVS-1000E test and Pelli-Robson chart, and color vision using the Farnsworth desaturated D15 and L'Anthony desaturated D15 tests. Structural analysis of the retina was performed using Spectral domain (SD) optical coherence tomography (OCT) with the Cirrus High definition (HD) OCT (Carl Zeiss Meditec Inc, Dublin, CA), which included three different protocols: macular protocol (for macular thickness analysis), RNFL protocol, and ganglion cell protocol (for individual analysis of this layer). 

110 LogMAR visual acuity (VA) was evaluated at three different contrast levels: 100% (HCVA,

111 using ETDRS chart), 2.50%, and 1.25% (LCVA, using Low-Contrast Sloan Letter Charts -

112 Precision Vision, LaSalle, IL-), The percentage indicating the level of contrast, i.e., 100%

113 representing black letters over white background and 1.25% light grey letters over white

114 background. All measurements were obtained under monocular vision and controlled lighting

115 conditions with best correction.

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Contrast sensitivity provides more complete information about visual function than visual acuity tests. CSV was evaluated in our patients using the Pelli-Robson chart and the CVS-1000E test. The Pelli-Robson chart comprises horizontal lines of capital letters organized into groups of three (triplets) with two triplets per line. Within each triplet, all letters have the same contrast. The contrast decreases from one triplet to the next, even within each line. All patients were evaluated under both monocular and binocular vision at a distance of 1 meter from the chart and under controlled fotopic conditions (85  $cd/m^2$ ). The score corresponding to the last triplet of letters seen by the patient was recorded. The CSV-1000E instrument is used worldwide for standardized CSV and glare testing. All patients were evaluated at a distance of 2.5 meters from the chart under monocular vision at 4 different spatial frequencies (3, 6, 12, and 18 cycles per degree [cpd]). The chart comprises four rows with 17 circular patches each. The patches present a grating that decreases in contrast moving from left to right across the row. The patient indicates whether the grating appears in the top patch or the bottom patch for each column. Each contrast value for each spatial frequency was transformed into a logarithmic scale according to standardized values. Color vision was assessed using the Color Vision Recorder (CVR) program. CVR software analyzes chromatic discrimination by classification of colors. The program includes the classic test of Farnsworth 100-hue (FM-100), Farnsworth - Munsell D15, and L'Anthony D15. All patients in the study were evaluated using the Farnsworth - Munsell D15 and L'Anthony D15 protocols and different output parameters such as the Confusion Index (C-index), the Color Confusion Index (CCI), the Confusion angle (Conf Ang), and the Scatter Index (S-index) were recorded.[19,20] The tests were performed under monocular vision. 

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Structural measurements of the retina were obtained using the Cirrus OCT device. The same experienced operator performed all scans and did not apply manual correction to the OCT output. We used an internal fixation target because it provides the highest reproducibility and rejected poor quality scans prior to data analysis. The Cirrus OCT macular cube 512 x 128 protocol provides a macular volume measure and retinal thickness values for nine areas. These areas include a central 1-mm circle representing the fovea, and inner and outer rings measuring 3 mm and 6 mm in diameter, respectively. The inner and outer rings are divided into four quadrants each. The Cirrus OCT optic disc protocol generates images with 200 linear scans enabling analysis of the RNFL of a 6-mm<sup>3</sup> area around the optic nerve. For each scan series of RNFL measurements, we assessed the average, superior, inferior, temporal, and nasal thickness. Cirrus segmentation analysis for retinal layers also provides measurements of the GCL thickness, evaluating six areas of the macular cube (superior, superonasal, inferonasal, inferior, inferotemporal, and superotemporal sectors) and measurements of the average and minimum GCL plus the inner plexiform layer (GCL + IPL) value of a set of 360 spokes, where each average represents the mean number of the pixels along that spoke that lies within the measurement annulus. The minimum is selected because the thinnest portion of the GCL + IPL in the perifoveal region is considered to indicate damage to the ganglion cells. All data analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL). Due to the parametric distribution of the data, differences between evaluations of PD patients and healthy subjects were compared using Student's t-test. The linear correlation between structural and functional parameters was determined using Pearson's correlation coefficient. Values of p < 0.05 were considered to indicate statistical significance. Each eye was considered separately, and one eye from each patient was randomly selected for analysis.
161	Results
162	Thirty-seven patients with PD and 37 healthy controls were included in the study. The mean age
163	of the patients with PD was 69 years (range: 58-74 years) and the mean age of the healthy
164	controls was 68 years (range: 60-76 years). Age (p=0.361), sex (p=0.441), and intraocular
165	pressure (p=0.720) did not differ significantly between healthy controls and patients with PD.
166	Mean time from diagnosis of PD was 13.2 years. The median Hoehn Yahr stage was 2.7, and the
167	stage of PD based on the UPDRS was 25.06 (range: 7-39; Table 1).
168	Treatment was divided into three different categories: "Drugs that enhance dopamine levels"
169	(carbidopa, levodopa and rasagiline), "dopaminergic drugs" (pramipexole, ropirinol, rotigotine),
170	and "other" (amitriptiline, propranolol, clonazepam). "Drugs that enhance dopamine levels" was
171	the most prescribed category (89% of patients) and combination therapy with levodopa and
172	carbidopa was the most frequent treatment (44%). Sixty-four percent of treatments were
173	categorized as "dopaminergic", most of which were used in combination with drugs included in
174	the previous category. A small percentage of patients (9%) were prescribed drugs with no
175	dopaminergic effects.
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	PARAMETER	CONTROLS	PARKINSON DISEASE	р
	Number of eyes (n)	37	37	-
	Age, years, range	68 (60–76)	69 (58–74)	0.361
	Men:Women (% of men)	24:13 (64.9)	23:14 (62.2)	0.441
	Intraocular Pressure	15.58 (2.71)	15.12 (2.98)	0.720
	Disease duration, years, mean (SD)	-	13.2 (5.77)	-
	Hoehn Yahr, mean (SD)	-	2.7 (0.64)	-
	UPDRS, mean (SD)	0.	25.06 (8.24)	-
2				
3	Functional parameters			
	1			
4	PD patients had a lower BC	VA at all three c	contrast levels of the ETDR	S chart compa
34 35	PD patients had a lower BC controls (0.18±0.26 in patie	EVA at all three c ents vs -0.065 $\pm$ 0	contrast levels of the ETDR 0.9 in controls at 100%, p=0	S chart companents of the second strength Science Science (1997) Science Scien
4 5	PD patients had a lower BC controls (0.18±0.26 in patie 0.44±0.13 at 2.50%, p=0.01	EVA at all three c ents vs $-0.065 \pm 0$ ; and $0.61\pm0.23$	contrast levels of the ETDR 0.9 in controls at 100%, p=0 vs 0.58±0.16 at 1.25%, p=0	S chart compan 0.001; 0.59±0.2 0.009). CSV wa
34 35 36 37	PD patients had a lower BC controls (0.18±0.26 in patie 0.44±0.13 at 2.50%, p=0.01 in patients at all four spatial	EVA at all three c ents vs $-0.065 \pm 0$ ; and $0.61\pm0.23$ I frequencies of t	contrast levels of the ETDR 0.9 in controls at 100%, p=0 vs 0.58±0.16 at 1.25%, p=0 he CSV 1000E chart (3, 6,	S chart compan 0.001; 0.59±0.2 0.009). CSV wa 12, and 18 cpd
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34 35 36 37 38	PD patients had a lower BC controls (0.18±0.26 in patie 0.44±0.13 at 2.50%, p=0.01 in patients at all four spatial analyzed based on the numb respectively). The Pelli Rob	EVA at all three c ents vs $-0.065 \pm 0$ ; and $0.61\pm0.23$ I frequencies of t ber of correct loc	contrast levels of the ETDR 0.9 in controls at 100%, p=0 vs 0.58±0.16 at 1.25%, p=0 he CSV 1000E chart (3, 6, calized gratings (p=0.001, < revealed a significant reduc	S chart compan 0.001; 0.59±0.2 0.009). CSV wa 12, and 18 cpd 0.001, <0.001, tion in CSV in
34 35 36 37 38 39	PD patients had a lower BC controls (0.18±0.26 in patie 0.44±0.13 at 2.50%, p=0.01 in patients at all four spatial analyzed based on the numb respectively). The Pelli Rob patients (1.71 in patients vs	EVA at all three c ents vs $-0.065 \pm 0$ ; and $0.61\pm0.23$ I frequencies of t ber of correct loc pson results also 1.89 in controls,	contrast levels of the ETDR 0.9 in controls at 100%, p=0 vs 0.58±0.16 at 1.25%, p=0 he CSV 1000E chart (3, 6, alized gratings (p=0.001, < revealed a significant reduc , p=0.02). Color vision (L'A	S chart company 0.001; 0.59±0.2 0.009). CSV wa 12, and 18 cpd 0.001, <0.001, tion in CSV in Anthony test in
34 35 36 37 38 39 90 91	PD patients had a lower BC controls (0.18±0.26 in patie 0.44±0.13 at 2.50%, p=0.01 in patients at all four spatial analyzed based on the numb respectively). The Pelli Rob patients (1.71 in patients vs also affected in PD. The res	EVA at all three c ents vs $-0.065 \pm 0$ ; and $0.61\pm0.23$ I frequencies of t ber of correct loc pson results also 1.89 in controls, sults are shown in	contrast levels of the ETDR 0.9 in controls at 100%, p=0 vs $0.58\pm0.16$ at $1.25\%$ , p=0 he CSV 1000E chart (3, 6, calized gratings (p=0.001, < revealed a significant reduc , p=0.02). Color vision (L'A n Table 2.	S chart compar 0.001; 0.59±0.2 0.009). CSV wa 12, and 18 cpd 0.001, <0.001, tion in CSV in anthony test in
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34 35 36 37 38 39 90 91 92 93	PD patients had a lower BC controls (0.18±0.26 in patie 0.44±0.13 at 2.50%, p=0.01 in patients at all four spatial analyzed based on the numb respectively). The Pelli Rob patients (1.71 in patients vs also affected in PD. The res	EVA at all three c ents vs $-0.065 \pm 0$ ; and $0.61\pm0.23$ I frequencies of t ber of correct loc pson results also 1.89 in controls, sults are shown in	contrast levels of the ETDR 0.9 in controls at 100%, p=0 vs $0.58\pm0.16$ at $1.25\%$ , p=0 he CSV 1000E chart (3, 6, calized gratings (p=0.001, < revealed a significant reduc , p=0.02). Color vision (L'A n Table 2.	S chart compar 2.001; 0.59±0.2 2.009). CSV wa 12, and 18 cpd 0.001, <0.001, tion in CSV in Anthony test ind
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	HEALTHY	CONTROLS	PARKINSON DISEASE PATIENTS		SIGNIFICANCE
	Mean	SD	Mean	SD	(P)
VA ETDRS 100	-0.06	0.096	0.18	0.26	0.001
VA ETDRS 2.5	0.44	0.13	0.59	0.22	0.010
VA ETDRS 1.25	0.58	0.16	0.62	0.23	0.009
Pelli Robson	1.89	0.11	1.71	0.17	0.002
CSV 1000 3 cpd	1.72	0.16	1.49	0.35	0.001*
CSV 1000 6 cpd	1.94	0.13	1.62	0.34	0.000*
CSV 1000 12 cpd	1.62	0.17	1.26	0.41	0.000*
CSV 1000 18 cpd	1.11	0.22	0.73	0.34	0.004*
Farnsworth AC CCI	1.11	0.22	0.73	0.34	0.851
Farnsworth C- index	1.10	0.20	1.24	0.42	0.093
Farnsworth CCI	1.07	0.12	1.14	0.24	0.110
Farnsworth Conf Angle	63.90	11.15	65.84	7.49	0.392
Farnsworth S-index	1.56	0.22	1.64	0.39	0.278
Farnsworth time	78.67	28.96	82.91	33.10	0.616
L'Anthony AC CCI	1.05	0.19	1.02	0.18	0.489
L' Anthony C-index	1.43	0.39	1.64	0.53	0.058
L' Anthony CCI	1.30	0.23	1.44	0.37	0.066
L' Anthony Conf Angle	62.31	14.74	71.91	9.25	0.002*
L' Anthony S-index	1.69	0.43	1.95	0.48	0.020
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OCT measurements indicated significant differences in superior macular sectors, in the outer inferior, outer temporal, and central macular thickness (results are shown in Table 2, Figure 1). The segmentation analysis revealed a significantly reduced GCL in PD patients in the superior  $(81.64\pm7.08 \ \mu\text{m} \text{ in patients vs } 84.55\pm4.32 \ \mu\text{m} \text{ in controls; } p=0.032)$  and superonasal sectors (81.04±7.23 µm vs 85.28±4.78 µm; p=0.029). The minimum GCL+IPL value was also reduced 

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204	(80.18±6.19 μm vs 82.45±3.60 μm; p=0.00	5). The RNFI	was significantly	reduced in the

temporal quadrant in PD patients (Table 3).

## 

	CONT	ROLS	PARKI DISE	NSON ASE	
Structural parameters	Mean	SD	Mean	SD	Р
Macular measurements					
Central macular thickness	254.75	17.903	248.96	17.765	0.028
Inner superior macular thickness	327.34	13.094	325.73	19.329	0.019
Inner nasal macular thickness	328.52	13.263	325.45	17.098	0.091
Inner inferior macular thickness	326.14	13.179	324.82	17.921	0.106
Inner temporal macular thickness	315.90	13.615	312.82	15.760	0.945
Outer superior macular thickness	284.76	9.418	279.44	17.981	0.008
Outer nasal macular thickness	302.41	12.167	299.18	17.064	0.074
Outer inferior macular thickness	277.79	10.755	273.76	16.798	0.045
Outer temporal macular thickness	271.52	10.992	266.23	18.987	0.013
Ganglion cell layer thickness					
Superior	84.55	4.323	81.61	7.087	0.032
Superonasal	85.28	4.780	81.04	7.234	0.029
Inferonasal	84.66	5.314	81.82	7.521	0.135
Inferior	84.34	5.052	81.91	6.252	0.389
Inferotemporal	85.79	4.003	83.73	4.860	0.233
Temporal	83.76	3.324	82.27	5.312	0.069
Average IPL+GCL	84.83	4.071	82.73	6.230	0.095
Min IPL+ GCL	82.45	3.601	80.18	6.194	0.005*
RNFL thickness					
Average	96.17	6.714	94.88	11.505	0.105
Superior	117.90	10.965	118.68	16.861	0.115
Nasal	73.59	12.724	72.40	15.182	0.345
Inferior	128.14	14.060	123.20	22.907	0.075
Temporal	64.97	8.218	61.48	10.553	0.027

## 208 Correlation between functional and structural parameters

209 CSV was the functional parameter most frequently associated with structural measurements in

210 PD. The Pelli Robson CSV results correlated with GCL thickness in all sectors, although the

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211	association was not strong (r < 0.5). The superonasal (r=0.40, p=0.010), inferonasal (r=0.40,
212	p=0.010), inferior (r=0.43, p=0.005), superotemporal sector (r=0.43, p=0.006), and average
213	GCL+IPL (r=0.45, p=0.004) values had the highest correlations. The Pelli Robson results also
214	correlated with the thickness in different sectors of the RNFL (average, superior, and inferior
215	sectors). Measurements with the CSV 1000E at different spatial frequencies correlated
216	significantly with most GCL measurements. The superonasal ( $r= 0.40$ , $p= 0.013$ ) and
217	superotemporal (r= 0.44, p= 0.006) thickness, average GCL +IPL thickness (r= 0.40, p= 0.012),
218	and the minimum GCL + IPL ( $r= 0.40$ , $p=0.011$ ) at a spatial frequency of 6 cpd; and the
219	superotemporal (r= 0.41, p= 0.01) thickness and the minimum GCL + IPL thickness (r= 0.43,
220	p=0.006) at a spatial frequency of 18 cpd had the strongest correlations between CSV 1000E and
221	GCL thickness. Spatial frequencies of 6 cpd and 18 cpd were strongly correlated with average
222	macular thickness (r= 0.79, p= 0.012; r= 0.77, p= 0.016, respectively) and macular volume (r=
223	0.78, p= 0.013; r= 0.78, p= 0.014, respectively).
224	Color vision assessed by the L'Anthony test was also associated with the structural parameters:
225	The C-index and CCI results were significantly correlated with all outer macular parameters and
226	most of the GCL measurements (see Table 4). A significant association between color vision and
227	the RNFL parameters was only found in isolated sectors. (see Table 4).
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		L'Anthony color test					
	C-index	р	CCI	р	S-index	р	
Macular thickness							
Central	-0.019	0.905	-0.059	0.716	-0.017	0.9	
Inner superior	-0.146	0.369	-0.119	0.463	-0.167	0.3	
Inner nasal	-0.055	0.735	-0.044	0.788	-0.040	0.8	
Inner inferior	-0.073	0.654	-0.064	0.697	-0.074	0.6	
Inner temporal	-0.049	0.764	-0.031	0.850	-0.126	0.4	
Outer superior	-0.377	0.017	-0.380	0.015	-0.271	0.0	
Outer nasal	-0.341	0.031	-0.323	0.042	-0.310	0.0	
Outer inferior	-0.360	0.022	-0.353	0.025	-0.375	0.0	
Outer temporal	-0.360	0.023	-0.361	0.022	-0.350	0.0	
Macular average	-0.691	0.019	-0.657	0.028	-0.709	0.0	
Macular volume	-0.686	0.020	-0.647	0.032	-0.709	0.0	
Ganglion cell layer thickness							
Superior	-0.380	0.015	-0.369	0.019	-0.287	0.0	
Superonasal	-0.383	0.015	-0.337	0.033	-0.350	0.0	
Inferonasal	-0.338	0.033	-0.313	0.049	-0.268	0.0	
Inferior	-0.341	0.031	-0.311	0.051	-0.282	0.0	
Inferotemporal	-0.252	0.116	-0.263	0.101	-0.203	0.2	
Temporal	-0.403	0.010	-0.437	0.005	-0.314	0.0	
Average IPL+ GCL	-0.381	0.015	-0.358	0.023	-0.319	0.0	
Minimum IPL+ GCL	-0.338	0.033	-0.326	0.040	-0.290	0.0	

The strongest correlation was between the average macular thickness and macular volume and
the L'Anthony CCI, C-index, and S-index results. No significant correlations were found

between the Farnsworth's test parameters and structural measurements.

The VA ETDRS results correlated strongly with average macular thickness and macular volume

(see Table 5, Figures 1 and 2). There were significant but mild associations between the GCL

240 parameters and VA at 100% (superonasal, inferonasal, and average GCL + IPL thickness, r=-

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241	0.38, p=0.016; r=-0.35, p=0.016; and r=0.35, p=0.029, respectively) and 2.50% (superonasal					
242	sector, r=-0.36, p=0.023).					
		Macular thickness	P value	Macular volume	P value	
	VA ETDRS 100	-0.765	0.006	-0.761	0.007	
	VA ETDRS 1.25	-0.718	0.013	-0.715	0.013	
	VA ETDRS 2.50	-0.738	0.010	-0.729	0.011	
2/13				-		

There was a significant correlation between Hoehn Yahr score and VA contrast level 2.50% (r=0.48, p=0.040), and CS measured with CSV 1000 at a space frequency of 12 cpd (r=-0.59, p=0.038). No correlations were detected between structural and disease severity parameters. 

#### **Discussion**

In the present study, we evaluated the visual function parameters and assessed the association between visual dysfunction and morphologic changes in the retina of 37 patients with PD. Parameters corresponding to VA at different contrast levels, and all CSV tests results were altered in PD patients in comparison with healthy subjects, prior to and after statistical correction for multiple tests. Moreover, contrast sensitivity was the most affected parameter in our study and correlated with most of the structural data. Color vision was measured with two different tests, the Farnsworth and L'Anthony 15 D tests. These tests provide information for differentiating subjects with severe loss of color vision from those with milder color defects or normal color vision, and also can be used to evaluate acquired loss of color vision. In our study, only the L'Anthony test results were significantly altered in PD patients. L'Anthony test is less saturated than the Farnsworth color test, thus it is designed to detect more subtle color deficiencies. Our patients performed worse than controls in both tests (higher C-index and S-

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index, reaching ranges similar to protanomalies) although only the differences in L'Anthony Sindex were statistically significant, indicating that our patients had a (subtle) protanomaly (Sindex of 1.95).

Previous studies have indicated that PD patients lose foveal contrast sensitivity to patterns to which normal observers are most sensitive (i.e., requiring the least contrast for detection).[8,9] Ganglion cells in the retina show adaptation to visual contrast and pool visual inputs over their receptive fields through an array of parallel bipolar cells with smaller receptive fields.[21] The parvo- and magnocellular ganglion cells are located in the RGC layer and take two different pathways for the identification of color and contrast at different frequencies.[22] RGC loss (as observed using SD-OCT) was recently identified as the cause of visual impairment in patients suffering from another neurodegenerative process, multiple sclerosis.[23] Thus, a similar process could be the cause of the contrast and color deficiencies in patients with PD. In addition, in the mammalian retina, color vision and contrast sensitivity are modulated through D1 and D2 receptors. These dopaminergic receptors are differentially located in the retinal layers and a complete lack of activation leads to signal dispersion and alterations in color vision and contrast sensitivity.[2] 

Alteration of the retinal layers in PD was first demonstrated in 2004.[24] Since then, various
studies have demonstrated different results.[3-5,24-27] Previous studies performed by our team
confirmed that both macular thickness and the RNFL were affected in patients with PD,
especially in the inferior and temporal quadrants.[4,5, 28] Moreover, Garcia-Martin et al
demonstrated that the inner retinal layers were most affected in these patients, and that the GCL
thickness was inversely correlated with disease duration and PD severity, and was predictive of
axonal damage in these patients.[29] The present study included a smaller number of patients,

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which may have affected the significance of our results compared to previous studies. Despite 283 284 the small number of subjects in the present study, however, we detected significant reductions in the macular, RNFL, and GCL thicknesses. A significant reduction in the temporal sectors of the 285 peripapillary RNFL thickness has been repeatedly observed by different groups [30, 31] and was 286 confirmed in the present study. Two recent studies, however, detected no differences in the 287 peripapillary RNFL thickness of PD patients compared to healthy controls using SD-OCT 288 [26,27] and one study only found significant differences in the nasal quadrant.[32] More studies 289 are required to clarify these contradictory observations. 290 In a previous study, we demonstrated that the retinal thickness corresponding to the 291 papillomacular bundle (as measured with the Axonal Analytics software for Spectralis OCT) 292 correlated (r>0.70) with some functional parameters (such as the mean defect and the pattern 293 standard deviation of the automated perimetry) in patients with PD.[33] The GCL was not 294 295 investigated at that time, however, and visual function parameters were reduced to perimetry and color vision measured with the Ishihara color test. The current study evaluated not only the 296 RNFL but also the GCL thickness, and more visual function parameters were analyzed. The 297 GCL correlated most with the visual function parameters: GCL thickness was directly associated 298 with VA and CSV measured at all different spatial frequencies, and inversely correlated with the 299 color vision indexes. Thus, GCL thinning is linked to color deficiencies, contrast sensitivity loss, 300 and lower vision at different contrast levels in PD patients. 301 302 The degree of correlation is usually classified as low (<0.30), moderate (0.30-0.70), or strong (>0.70). Our results revealed a low and moderate degree of correlation between most parameters, 303

volume, however, were strongly associated with functional parameters (VA, CS, and L'Anthony

consistent with findings in other neurodegenerative diseases.[34] Macular thickness and macular

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CCI, C-index, and S-index). This strong association, to the best of our knowledge, has not been previously demonstrated in PD.

There are very few studies of the correlation between functional and structural parameters in PD patients. Adam et al [14] demonstrated a significant reduction in the inner retinal layer complex (RNFL + GCL + IPL) in PD patients, but no association with contrast sensitivity (measured with the Pelli Robson chart). A very recent study by Kaur et al [15] demonstrated a correlation between functional parameters and GCL thinning, consistent with our results. Kaur et al, however, found no significant alterations in VA or color vision in PD patients and the severity of the disease was not correlated with structural parameters, in contrast to other studies that demonstrate an association between macular and GCL thickness and disease duration and severity.[28,29] Although the severity of the disease in our sample (based on the Hoehn Yahr scale) was similar to that in Kaur's study, the duration of the disease in our study was higher than that in Kaur's patients (13 years vs 5 years), which may account for some of the differences in the results between the two studies. These discrepancies (and similarities) support the need for more studies on this topic. Our results, together with previously published studies, [15, 29] suggest that the GCL could be a reliable indicator of structural alterations in the retina of PD patients, demonstrating a significant correlation with functional tests in these patients. The results of the present study have important implications for clinical diagnosis and functional deficits in patients with PD, and highlight the importance of visual function tests in the evaluation of these patients.

In conclusion, visual dysfunction was significantly correlated with morphologic parameters in PD patients. PD patients present with a reduction in macular, RNFL, and GCL thickness, with changes in the GCL being most closely associated with visual dysfunction.

1 2		
3 4 5	329 330	This research received no specific grant from any funding agency in the public, commercial or not-for- profit sectors.
6 7	331	Competing interest:
8 0	332	The authors disclose no conflict of interest.
10	333	Data sharing:
11 12	334	No additional data available.
13	335	Contributorship:
14 15		
16 17	336	V. Polo: Research project: organization. Statistical analysis and Manuscript: Review and
18 19 20	337	critique.
21 22 22	338	M. Satue: Research project: Conception, design, organization and execution. Statistical analysis:
23 24 25	339	Review and critique. Manuscript: Writing of the first draft, review and critique.
26 27 28	340	MJ Rodrigo: Research project: organization and execution. Statistical analysis: Review and
29 30	341	critique. Manuscript: Writing of the first draft, review and critique.
31 32 33	342	S. Otin: Research project: organization and execution. Statistical analysis: Review and critique.
34 35	343	Manuscript: review and critique.
36 37 38	344	R. Alarcia: Research project: organization and execution. Statistical analysis: Review and
39 40	345	critique. Manuscript: review and critique.
41 42 43	346	MP. Bambo: Research project: execution. Statistical analysis: Review and critique. Manuscript:
44 45	347	review and critique.
46 47 48	348	MI. Fuertes: Research project: execution. Statistical analysis: Review and critique. Manuscript:
49 50 51	349	review and critique.
52 53	350	JM. Larrosa: Research project: execution. Statistical analysis: Review and critique. Manuscript:
54 55 56	351	review and critique.
57 58 59 60	352	LE. Pablo: Research project: execution. Statistical analysis: Review and critique. Manuscript:
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6 7	441	Figure 1 Correlation between the average macular thickness and visual acuity as measured with
8 9	442	ETDRS optotipe at a contrast level of 100% in patients with Parkinson's disease.
10 11 12 13	443	
14 15	444	Figure 2: Correlation between macular volume and visual acuity as measured with ETDRS
16 17 18	445	optotipe at a contrast level of 100% in patients with Parkinson's disease.
19 20 21	446	
22 23	447	Table 1: Epidemiologic and disease characteristics of patients with PD and healthy subjects, and
24 25 26	448	statistical significance (P). Abbreviations: SD, standard deviation; UPDRS, Unified Parkinson
27 28	449	Disease Rating Scale.
29 30 31	450	
32 33 34	451	Table 2: Mean and standard deviation (SD) of visual functional parameters in healthy controls
35 36	452	and subjects with Parkinson disease. Results in bold letters indicate statistical significance
37 38 39	453	(p<0.05). The asterisk indicates those values with statistical significance after Bonferroni
40 41	454	correction for multiple tests (p<0.0125 for CSV 1000E measurements; p<0.0083 for Farnsworth
42 43	455	and L'Anthony tests). Abbreviations: VA, visual acuity; ETDRS, early treatment diabetic
44 45 46	456	retinopathy study; cpd, cycles per degree; AC CCI, age corrected color confusion index; CCI,
47 48	457	color confusion index; C-index, confusion index; Conf Angle, confusion angle; S-index, scatter
49 50 51	458	index; PD, Parkinson disease.
52 53	459	
54 55	460	Table 3: Mean and standard deviation (SD) of structural parameters (retinal nerve fiber layer,
56 57 58 59 60	461	ganglion cell layer and macular thicknesses) obtained with the Cirrus HD optical coherence

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tomography device in healthy controls and subjects with Parkinson disease. Bold letters indicate statistical significance (p < 0.05). The asterisk indicates those values with statistical significance after Bonferroni correction for multiple tests (p < 0.0055 for macular measurements; p < 0.0062 for ganglion cell measurements and p<0.01 for RNFL measurements). Abbreviations: IPL, inner plexiform layer; GCL, ganglion cell layer; RNFL, retinal nerve fiber layer; HD, high definition. Table 4: Correlation between macular and ganglion cell layer structural measurements and color vision evaluated with L'Anthony color test in patients with Parkinson disease. Data in bold type correspond to statistically significant correlations (p value <0.05). Abbreviations: GCL, ganglion cell layer; IPL, inner plexiform layer; C-index, Confusion index; CCI, color confusion index; S-index, Scatter index. Table 5: Correlation between visual acuity measured with ETDRS chart at different levels of contrast (in %) and macular structural measurements (thickness and volume) in patients with Parkinson disease. Correlation data in bold type are statistically significant (p value <0.05). Abbreviations: VA, visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study. For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml







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## Figure 2: Correlation between macular volume and visual acuity as measured with ETDRS optotipe at a contrast level of 100% in patients with Parkinson's disease. 119x102mm (300 x 300 DPI)

STROBE Statement-	-Chec	klist of items that should be included in reports of <i>case-control studies</i>
	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract
		Check. This included in the abstract, methods, line 1
		(b) Provide in the abstract an informative and balanced summary of what was done
		and what was found
		Check. This is included in the abstract. Methods, from line 2 to results section line 9
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
		Check. This is included in the introduction. Paragraph 2.
Objectives	3	State specific objectives including any prespecified hypotheses Check. This is
00000000	Ő	included in the introduction. Paragraph 3.
Methods		
Study design	4	Present key elements of study design early in the paper
		Check. This is included in Methods, paragraph 1-3.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment.
0		exposure, follow-up, and data collection
		Check. This is included in Methods, paragraph 1-3.
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment
	, e	and control selection. Give the rationale for the choice of cases and controls
		Check. This is included in Methods, paragraph 2
		(b) For matched studies give matching criteria and the number of controls per case
		Check. This is included in Methods, paragraph 1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect
		modifiers. Give diagnostic criteria, if applicable
		Check. Outcomes and variables are explained in Methods, paragraphs 4-8
Data sources/	8*	For each variable of interest, give sources of data and details of methods of
measurement		assessment (measurement). Describe comparability of assessment methods if there is
		more than one group
		Check. Details of measurements are included in paragraphs 4-8.
Bias	9	Describe any efforts to address potential sources of bias
		Check. This is included in paragraph 8, line 3-4.
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable
		describe which groupings were chosen and why
		Check. Quantitative variables are explained in Methods, paragraphs 4-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding
		Check. This is included in methods, paragraph 9
		(b) Describe any methods used to examine subgroups and interactions Not
		applicable.
		(c) Explain how missing data were addressed Not applicable
		(d) If applicable, explain how matching of cases and controls was addressed Not
		applicable
		- **

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially
		eligible, examined for eligibility, confirmed eligible, included in the study,
		completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
		This is a cross sectional study. Inclusion criteria were explained in methods. All
		elegible subjects were included in the study (37) as already explained, all completed
		the evaluation.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and
		information on exposures and potential confounders Check. This is included in
		Results, paragraph 1-2 and table 1.
		(b) Indicate number of participants with missing data for each variable of interest
		Not applicable.
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure
		Check. Numbers and results of each variable are included in results.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and
		their precision (eg, 95% confidence interval). Make clear which confounders were
		adjusted for and why they were included
		Check. Main results include statistical results prior and post multiple comparisons
		adjustment.
		(b) Report category boundaries when continuous variables were categorized Check.
		Category of correlation is explained in discussion, paragraph 5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a
		meaningful time period Not applicable

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Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity analyses
		Not applicable
Discussion		
Key results	18	Summarise key results with reference to study objectives Check. This is included in results, paragraph 1.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.
		Discuss both direction and magnitude of any potential bias
		Check, this is mentioned in paragraph 3 and 6.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity
		of analyses, results from similar studies, and other relevant evidence
		Check. This is included and discussed along the discussion section.
Generalisability	21	Discuss the generalisability (external validity) of the study results Check. This is included and
		discussed along the discussion section
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable,
		for the original study on which the present article is based Check. Not applicable.

\*Give information separately for cases and controls.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

# **BMJ Open**

## Visual dysfunction and its correlation with retinal changes in patients with Parkinson disease

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15 16	4	Polo V <sup>1,2</sup> , Satue M <sup>1,2</sup> , Rodrigo MJ <sup>1</sup> , Otin S <sup>1,2</sup> , Alarcia R <sup>1,3</sup> , Bambo MP <sup>1,2</sup> , Fuertes MI <sup>1,2</sup> , Larrosa
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38 39	15 16	RUNNING TITLE: OCT and visual dysfunction in Parkinson disease
40	17	STUDY DESIGN AND SETTING: An observational prospective study, carried out at Miguel
41 42	18	Servet University Hospital, in Zaragoza, Spain.
43 44	19	KEY WORDS: Parkinson disease, visual function, contrast sensitivity, ganglion cell layer.
44 45 46	20	WORD COUNT: 2500 words.
47 49	21	All subjects provided detailed consent to participate in this study, which was conducted in
48 49	22	accordance with the guidelines established by the Ethics Committee of the Miguel Servet
50 51	23	Hospital and based on the principles of the Declaration of Helsinki.
51 52	24 25	This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.
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$\begin{array}{c} 33\\ 34\\ 35\\ 36\\ 37\\ 38\\ 39\\ 40\\ 41\\ 42\\ 43\\ 44\\ 54\\ 45\\ 46\\ 47\\ 48\\ 9\\ 50\\ 1\\ 52\\ 53\\ 55\\ 57\\ 58\\ 9\\ 60\\ \end{array}$	14 15 16 17 18 19 20 21 22 23 24 25	<ul> <li>Email: mariasatue@gmail.com</li> <li>Telephone: 0034.976.76.55.58</li> <li>RUNNING TITLE: OCT and visual dysfunction in Parkinson disease</li> <li>STUDY DESIGN AND SETTING: An observational prospective study, carried out at Miguel</li> <li>Servet University Hospital, in Zaragoza, Spain.</li> <li>KEY WORDS: Parkinson disease, visual function, contrast sensitivity, ganglion cell layer.</li> <li>WORD COUNT: 2500 words.</li> <li>All subjects provided detailed consent to participate in this study, which was conducted in accordance with the guidelines established by the Ethics Committee of the Miguel Servet Hospital and based on the principles of the Declaration of Helsinki.</li> <li>This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.</li> </ul>

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#### 6

#### 34 <u>Abstract</u>

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,	35	Objectives: To evaluate visual dysfunction and its correlation with structural changes in the
2	36	retina in patients with Parkinson disease (PD).
	37	Methods: Patients with PD (n=37) and controls (n=37) were included in an observational cross-
,	38	sectional study and underwent visual acuity (VA), color vision (using the Farnsworth and
; ,	39	L'Anthony desaturated D15 color tests), and contrast sensitivity vision (CSV; using the Pelli
5	40	Robson chart and CSV 1000E test) evaluation to measure visual dysfunction. Structural
)	41	measurements of the retinal nerve fiber layer (RNFL), and macular and ganglion cell layer
)	42	(GCL) thicknesses were obtained using spectral domain optical coherence tomography (SD-
2	43	OCT). Comparison of obtained data and correlation analysis between functional and structural
5	44	results were performed.
5	45	Results: VA (in all different contrast levels) and all CSV spatial frequencies were significantly
) ,	46	worse in PD patients than in controls (P < $0.05$ ). Color vision was significantly affected
5	47	(p<0.05) based on the L'Anthony color test. Macular thinning was detected in the central, outer
)	48	(inferior and temporal), and superior (inner and outer) sectors (p<0.05), and the RNFL had
)	49	significant thinning in the temporal quadrant (p<0.05). Significant GCL loss was observed in the
2	50	superior and superonasal sectors and the minimum GCL + inner plexiform layer (p<0.05). CSV
5	51	was the functional parameter most strongly correlated with structural measurements in PD.
, ,	52	Color vision was associated with most GCL measurements. Macular thickness was strongly
5	53	correlated with macular volume and functional parameters ( $r > 0.70$ , $p < 0.05$ ).
}	54	Conclusions: Patients with PD had visual dysfunction that correlated with structural changes
)	55	evaluated by SD-OCT. Macular and GCL measurements may be reliable indicators of visual
)	56	impairment in PD patients.
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12	61	The strengths of this study should be resumed by the following bullet points:
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15 16	62	- We detected alteration in VA (at different contrast levels), CSV and CV in PD patients.
17	63	CSV correlated with most of the structural data.
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19	64	- We detected significant reductions in the macular, RNFL, and GCL thicknesses. The
20	<u>ر ٦</u>	CCL correlated most with the viewel function response
21	65	GCL correlated most with the visual function parameters.
22	66	- There are only 2 other published articles evaluating the association between visual
23 24		
24	67	dysfunction and morphologic parameters. Results provided by these previous studies
26	60	differ from our results, possibly due to different measurement methods and sample size
27	08	differ from our results, possibly due to different measurement methods and sample size.
28	69	- CV in our study was assessed by L'Anthony and Farnsworth D15 color tests, which may
29		
30	70	provide more specific information about color deficiencies. These tests are not commonly
51 22	71	used to evaluate color deficiencies in PD patients
33	/1	used to evaluate color denciencies in r D patients.
34	72	- Macular thickness and macular volume were strongly associated with functional
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6	73	parameters. This is the first time such a strong correlation is reported $(r>0.70)$ .
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#### 75 <u>Introduction</u>

76	Foveal vision alterations are associated with Parkinson disease (PD), and seem to be caused by
77	dysfunction of the intraretinal dopaminergic circuitry and final retinal output to the brain.[1]
78	Recent studies demonstrated retinal thinning in PD patients compared with healthy subjects.[2-5]
79	Several studies report a correlation between functional disability and axonal loss observed in the
80	optic nerve in multiple sclerosis, another neurodegenerative process.[6,7] PD patients are also
81	reported to have decreased contrast sensitivity and color vision, and altered visual evoked
82	potentials.[1,8-13] To our knowledge, however, very few studies have assessed visual
83	dysfunction in PD and its correlation with morphologic parameters.[14,15]
84	In the present study, we evaluated visual acuity (VA) using an Early Treatment Diabetic
85	Retinopathy Study (ETDRS) chart, contrast sensitivity vision (CSV) using the CSV-1000E test
86	and Pelli-Robson chart, and color vision using the Farnsworth and L'Anthony tests in PD
87	patients and healthy controls to examine the association between visual dysfunction and
88	morphologic parameters.
89	
90	Material and methods

91 Thirty-seven eyes of 37 patients with definite PD and 37 eyes of 37 age- and sex-matched
92 healthy individuals were recruited for the study. The study was performed at Miguel Servet
93 University Hospital in Zaragoza, Spain. All procedures adhered to the tenets of the Declaration
94 of Helsinki, and all participants provided informed consent to participate in the study.

The diagnosis of PD was based on standard clinical and neuroimaging criteria.[16] Information about disease severity was assessed using the Hoehn Yahr scale [17] and the Unified Parkinson Disease Rating Scale part III score (UPDRS III) [18]. Disease duration and treatment were recorded. Exclusion criteria were the presence of significant refractive errors (>5 diopters of spherical equivalent refraction or 3 diopters of astigmatism); intraocular pressure  $\geq 21$  mmHg; media opacifications; concomitant ocular diseases, including history of glaucoma or retinal pathology; and systemic conditions that could affect the visual system. The healthy controls had no history and no evidence of ocular or neurologic disease of any nature; their best-corrected visual acuity (BCVA) was >20/30 based on the Snellen scale. All subjects underwent a complete neuro-ophthalmic evaluation that included pupillary, anterior segment, and funduscopic examination. Visual function was assessed by evaluating BCVA using an ETDRS chart, CSV using the CVS-1000E test and Pelli-Robson chart, and color vision using the Farnsworth desaturated D15 and L'Anthony desaturated D15 tests. Structural analysis of the retina was performed using Spectral domain (SD) optical coherence tomography (OCT) with the Cirrus High definition (HD) OCT (Carl Zeiss Meditec Inc, Dublin, CA), which included three different protocols: macular protocol (for macular thickness analysis), RNFL protocol, and ganglion cell protocol (for individual analysis of this layer). LogMAR visual acuity (VA) was evaluated at three different contrast levels: 100% (HCVA, using ETDRS chart), 2.50%, and 1.25% (LCVA, using Low-Contrast Sloan Letter Charts -Precision Vision, LaSalle, IL-), The percentage indicating the level of contrast, i.e., 100% representing black letters over white background and 1.25% light grey letters over white background. All measurements were obtained under monocular vision and controlled lighting conditions with best correction.

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118	Contrast sensitivity provides more complete information about visual function than visual acuity
119	tests. CSV was evaluated in our patients using the Pelli-Robson chart and the CVS-1000E test.
120	The Pelli-Robson chart comprises horizontal lines of capital letters organized into groups of
121	three (triplets) with two triplets per line. Within each triplet, all letters have the same contrast.
122	The contrast decreases from one triplet to the next, even within each line. All patients were
123	evaluated under both monocular and binocular vision at a distance of 1 meter from the chart and
124	under controlled fotopic conditions (85 $cd/m^2$ ). The score corresponding to the last triplet of
125	letters seen by the patient was recorded.
126	The CSV-1000E instrument is used worldwide for standardized CSV and glare testing. All
127	patients were evaluated at a distance of 2.5 meters from the chart under monocular vision at 4
128	different spatial frequencies (3, 6, 12, and 18 cycles per degree [cpd]). The chart comprises four
129	rows with 17 circular patches each. The patches present a grating that decreases in contrast
130	moving from left to right across the row. The patient indicates whether the grating appears in the
131	top patch or the bottom patch for each column. Each contrast value for each spatial frequency
132	was transformed into a logarithmic scale according to standardized values.
133	Color vision was assessed using the Color Vision Recorder (CVR) program. CVR software
134	analyzes chromatic discrimination by classification of colors. The program includes the classic
135	test of Farnsworth 100-hue (FM-100), Farnsworth - Munsell D15, and L'Anthony D15. All
136	patients in the study were evaluated using the Farnsworth - Munsell D15 and L'Anthony D15
137	protocols and different output parameters such as the Confusion Index (C-index), the Color
138	Confusion Index (CCI), the Confusion angle (Conf Ang), and the Scatter Index (S-index) were
139	recorded.[19,20] The tests were performed under monocular vision.

140	Structural measurements of the retina were obtained using the Cirrus OCT device. The same
141	experienced operator performed all scans and did not apply manual correction to the OCT
142	output. We used an internal fixation target because it provides the highest reproducibility and
143	rejected poor quality scans prior to data analysis. The Cirrus OCT macular cube 512 x 128
144	protocol provides a macular volume measure and retinal thickness values for nine areas. These
145	areas include a central 1-mm circle representing the fovea, and inner and outer rings measuring 3
146	mm and 6 mm in diameter, respectively. The inner and outer rings are divided into four
147	quadrants each. The Cirrus OCT optic disc protocol generates images with 200 linear scans
148	enabling analysis of the RNFL of a 6-mm <sup>3</sup> area around the optic nerve. For each scan series of
149	RNFL measurements, we assessed the average, superior, inferior, temporal, and nasal thickness.
150	Cirrus segmentation analysis for retinal layers also provides measurements of the GCL thickness,
151	evaluating six areas of the macular cube (superior, superonasal, inferonasal, inferior,
152	inferotemporal, and superotemporal sectors) and measurements of the average and minimum
153	GCL plus the inner plexiform layer (GCL + IPL) value of a set of 360 spokes, where each
154	average represents the mean number of the pixels along that spoke that lies within the
155	measurement annulus. The minimum is selected because the thinnest portion of the GCL + IPL
156	in the perifoveal region is considered to indicate damage to the ganglion cells.
157	All data analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL).
158	Due to the parametric distribution of the data, differences between evaluations of PD patients
159	and healthy subjects were compared using Student's t-test. To avoid a high false positive rate,
160	the Bonferroni correction for multiple comparisons was calculated. The level of significance for
161	each variable was established based on Bonferroni calculations.

The linear correlation between structural and functional parameters was determined using Pearson's correlation coefficient. Values of p < 0.05 were considered to indicate a significant correlation. Each eye was considered separately, and one eye from each patient was randomly selected for analysis.

166 <u>Results</u>

Thirty-seven patients with PD and 37 healthy controls were included in the study. The mean age of the patients with PD was 69 years (range: 58–74 years) and the mean age of the healthy controls was 68 years (range: 60-76 years). Age (p=0.361), sex (p=0.441), and intraocular pressure (p=0.720) did not differ significantly between healthy controls and patients with PD. Mean time from diagnosis of PD was 13.2 years. The median Hoehn Yahr stage was 2.7, and the stage of PD based on the UPDRS III was 25.06 (range: 7-39; Table 1). Treatment was divided into three different categories: "Drugs that enhance dopamine levels" (carbidopa, levodopa and rasagiline), "dopaminergic drugs" (pramipexole, ropirinol, rotigotine), and "other" (amitriptiline, propranolol, clonazepam). "Drugs that enhance dopamine levels" was the most prescribed category (89% of patients) and combination therapy with levodopa and carbidopa was the most frequent treatment (44%). Sixty-four percent of treatments were categorized as "dopaminergic", most of which were used in combination with drugs included in the previous category. A small percentage of patients (9%) were prescribed drugs with no dopaminergic effects. 

CONTROLS	PARKINSON DISEASE	р		
37	37	-		
68 (60–76)	69 (58–74)	0.361		
24:13 (64.9)	23:14 (62.2)	0.441		
15.58 (2.71)	15.12 (2.98)	0.720		
-	13.2 (5.77)	-		
-	2.7 (0.64)	-		
-	25.06 (8.24)	-		
	CONTROLS 37 68 (60–76) 24:13 (64.9) 15.58 (2.71) - - - -	CONTROLS         PARKINSON DISEASE           37         37           68 (60-76)         69 (58-74)           24:13 (64.9)         23:14 (62.2)           15.58 (2.71)         15.12 (2.98)           -         13.2 (5.77)           -         2.7 (0.64)           -         25.06 (8.24)		

#### 188 Functional parameters

PD patients had a lower BCVA at all three contrast levels of the ETDRS chart compared to the controls (0.18 $\pm$ 0.26 in patients vs -0.065  $\pm$  0.9 in controls at 100%, p=0.001; 0.59 $\pm$ 0.21 vs 0.44±0.13 at 2.50%, p=0.010; and 0.61±0.23 vs 0.58±0.16 at 1.25%, p=0.009). CSV was affected in patients at all four spatial frequencies of the CSV 1000E chart (3, 6, 12, and 18 cpd) when analyzed based on the number of correct localized gratings (p=0.001, <0.001, <0.001, and 0.004 respectively). The Pelli Robson results also revealed a significant reduction in CSV in PD patients (1.71 in patients vs 1.89 in controls, p=0.02). Color vision (Conf Angle in L'Anthony test) was also affected in PD. The results are shown in Table 2. 

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	HEALTHY CONTROLS		PARKINSON DISEASE PATIENTS		SIGNIFICANCE
	Mean	SD	Mean	SD	( <b>P</b> )
VA ETDRS 100	-0.06	0.096	0.18	0.26	0.001*
VA ETDRS 2.5	0.44	0.13	0.59	0.22	0.010*
VA ETDRS 1.25	0.58	0.16	0.62	0.23	0.009*
Pelli Robson	1.89	0.11	1.71	0.17	0.002*
CSV 1000 3 cpd	1.72	0.16	1.49	0.35	0.001*
CSV 1000 6 cpd	1.94	0.13	1.62	0.34	<0.001*
CSV 1000 12 cpd	1.62	0.17	1.26	0.41	<0.001*
CSV 1000 18 cpd	1.11	0.22	0.73	0.34	0.004*
Farnsworth AC CCI	1.11	0.22	0.73	0.34	0.851
Farnsworth C- index	1.10	0.20	1.24	0.42	0.093
Farnsworth CCI	1.07	0.12	1.14	0.24	0.110
Farnsworth Conf Angle	63.90	11.15	65.84	7.49	0.392
Farnsworth S-index	1.56	0.22	1.64	0.39	0.278
Farnsworth time	78.67	28.96	82.91	33.10	0.616
L'Anthony AC CCI	1.05	0.19	1.02	0.18	0.489
L' Anthony C-index	1.43	0.39	1.64	0.53	0.058
L' Anthony CCI	1.30	0.23	1.44	0.37	0.066
L' Anthony Conf Angle	62.31	14.74	71.91	9.25	0.002*
L' Anthony S-index	1.69	0.43	1.95	0.48	0.020
L' Anthony time	77.14	25.99	84.09	39.31	0.431

#### ) --

#### 199 Structural parameters

200 Based on Bonferroni corrections, OCT measurements indicated a significant difference in the minimum GCL+IPL value (80.18±6.19 µm vs 82.45±3.60 µm; p=0.005). However, we observed 201 202 a clear tendency towards a reduction in superior macular sectors, in the outer inferior, outer 203 temporal, and central macular thickness in PD patients compared to controls: the p value for 204 these variables was <0.05 but did not meet Bonferroni significance (results are shown in Table 205 2). The segmentation analysis revealed a tendency towards reduced GCL in PD patients in the 206 superior (81.64±7.08 µm in patients vs 84.55±4.32 µm in controls; p=0.032) and superonasal 207 sectors (81.04±7.23 µm vs 85.28±4.78 µm; p=0.029); and the RNFL was reduced in the

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temporal quadrant in PD patients (Table 3). These parameters however, did not meet the level of

significance stablished by Bonferroni correction. 

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	CONT	ROLS	PARKI DISE	NSON ASE	
Structural parameters	Mean	SD	Mean	SD	Р
Macular measurements					
Central macular thickness	254.75	17.903	248.96	17.765	0.028
Inner superior macular thickness	327.34	13.094	325.73	19.329	0.019
Inner nasal macular thickness	328.52	13.263	325.45	17.098	0.091
Inner inferior macular thickness	326.14	13.179	324.82	17.921	0.106
Inner temporal macular thickness	315.90	13.615	312.82	15.760	0.945
Outer superior macular thickness	284.76	9.418	279.44	17.981	0.008
Outer nasal macular thickness	302.41	12.167	299.18	17.064	0.074
Outer inferior macular thickness	277.79	10.755	273.76	16.798	0.045
Outer temporal macular thickness	271.52	10.992	266.23	18.987	0.013
Ganglion cell layer thickness					
Superior	84.55	4.323	81.61	7.087	0.032
Superonasal	85.28	4.780	81.04	7.234	0.029
Inferonasal	84.66	5.314	81.82	7.521	0.135
Inferior	84.34	5.052	81.91	6.252	0.389
Inferotemporal	85.79	4.003	83.73	4.860	0.233
Temporal	83.76	3.324	82.27	5.312	0.069
Average IPL+GCL	84.83	4.071	82.73	6.230	0.095
Min IPL+ GCL	82.45	3.601	80.18	6.194	0.005
RNFL thickness					
Average	96.17	6.714	94.88	11.505	0.105
Superior	117.90	10.965	118.68	16.861	0.115
Nasal	73.59	12.724	72.40	15.182	0.345
Inferior	128.14	14.060	123.20	22.907	0.075
Temporal	64.97	8.218	61.48	10.553	0.027

CSV was the functional parameter most frequently associated with structural measurements in

PD. The Pelli Robson CSV results correlated with GCL thickness in all sectors, although the

Correlation between functional and structural parameters

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215	association was not strong (r < 0.5). The superonasal (r=0.40, p=0.010), inferonasal (r=0.40,
216	p=0.010), inferior (r=0.43, p=0.005), superotemporal sector (r=0.43, p=0.006), and average
217	GCL+IPL (r=0.45, p=0.004) values had the highest correlations. The Pelli Robson results also
218	correlated with the thickness in different sectors of the RNFL (average, superior, and inferior
219	sectors). Measurements with the CSV 1000E at different spatial frequencies correlated
220	significantly with most GCL measurements. The superonasal ( $r= 0.40$ , $p= 0.013$ ) and
221	superotemporal (r= 0.44, p= 0.006) thickness, average GCL +IPL thickness (r= 0.40, p= 0.012),
222	and the minimum GCL + IPL ( $r= 0.40$ , $p=0.011$ ) at a spatial frequency of 6 cpd; and the
223	superotemporal ( $r= 0.41$ , $p= 0.01$ ) thickness and the minimum GCL + IPL thickness ( $r= 0.43$ ,
224	p=0.006) at a spatial frequency of 18 cpd had the strongest correlations between CSV 1000E and
225	GCL thickness. Spatial frequencies of 6 cpd and 18 cpd were strongly correlated with average
226	macular thickness (r= 0.79, p= 0.012; r= 0.77, p= 0.016, respectively) and macular volume (r=
227	0.78, p= 0.013; r= 0.78, p= 0.014, respectively, Figure 1).
228	Color vision assessed by the L'Anthony test was also associated with the structural parameters:
229	The C-index and CCI results were significantly correlated with all outer macular parameters and
230	most of the GCL measurements (see Table 4). A significant association between color vision and
231	the RNFL parameters was only found in isolated sectors. (see Table 4).
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		L'Anthony color test				
	C-index	р	CCI	р	S-index	р
Macular thickness						
Central	-0.019	0.905	-0.059	0.716	-0.017	0.9
Inner superior	-0.146	0.369	-0.119	0.463	-0.167	0.30
Inner nasal	-0.055	0.735	-0.044	0.788	-0.040	0.80
Inner inferior	-0.073	0.654	-0.064	0.697	-0.074	0.64
Inner temporal	-0.049	0.764	-0.031	0.850	-0.126	0.43
Outer superior	-0.377	0.017	-0.380	0.015	-0.271	0.09
Outer nasal	-0.341	0.031	-0.323	0.042	-0.310	0.0
Outer inferior	-0.360	0.022	-0.353	0.025	-0.375	0.0
Outer temporal	-0.360	0.023	-0.361	0.022	-0.350	0.02
Macular average	-0.691	0.019	-0.657	0.028	-0.709	0.0
Macular volume	-0.686	0.020	-0.647	0.032	-0.709	0.0
Ganglion cell layer thickness						
Superior	-0.380	0.015	-0.369	0.019	-0.287	0.0
Superonasal	-0.383	0.015	-0.337	0.033	-0.350	0.02
Inferonasal	-0.338	0.033	-0.313	0.049	-0.268	0.09
Inferior	-0.341	0.031	-0.311	0.051	-0.282	0.0
Inferotemporal	-0.252	0.116	-0.263	0.101	-0.203	0.20
Temporal	-0.403	0.010	-0.437	0.005	-0.314	0.04
Average IPL+ GCL	-0.381	0.015	-0.358	0.023	-0.319	0.04
Minimum IPL+ GCL	-0.338	0.033	-0.326	0.040	-0.290	0.0

The strongest correlation was between the average macular thickness and macular volume and 

the L'Anthony CCI, C-index, and S-index results. No significant correlations were found

between the Farnsworth's test parameters and structural measurements.

The VA ETDRS results correlated strongly with average macular thickness and macular volume

(see Table 5, Figures 2 and 3). There were significant but mild associations between the GCL

parameters and VA at 100% (superonasal, inferonasal, and average GCL + IPL thickness, r=-

245 0.38, p=0.016; r=-0.35, p=0.016; and r=0.35, p=0.029, respectively) and 2.50% (superonasal

246 sector, r=-0.36, p=0.023).

	Macular thickness	P value	Macular volume	P value
VA ETDRS 100	-0.765	0.006	-0.761	0.007
VA ETDRS 1.25	-0.718	0.013	-0.715	0.013
VA ETDRS 2.50	-0.738	0.010	-0.729	0.011

There was a significant correlation between Hoehn Yahr score and VA contrast level 2.50% (r=0.48, p=0.040), and CS measured with CSV 1000 at a space frequency of 12 cpd (r=-0.59, p=0.038). No correlations were detected between structural and disease severity parameters.

#### 251 Discussion

In the present study, we evaluated the visual function parameters and assessed the association between visual dysfunction and morphologic changes in the retina of 37 patients with PD. Parameters corresponding to VA at different contrast levels, and all CSV tests results were altered in PD patients in comparison with healthy subjects, prior to and after statistical correction for multiple tests. Moreover, contrast sensitivity was the most affected parameter in our study and correlated with most of the structural data. Color vision was measured with two different tests, the Farnsworth and L'Anthony 15 D tests. These tests provide information for differentiating subjects with severe loss of color vision from those with milder color defects or normal color vision, and also can be used to evaluate acquired loss of color vision. In our study, only the L'Anthony Confusion Angle was significantly altered in PD patients. L'Anthony test is less saturated than the Farnsworth color test, thus it is designed to detect more subtle color deficiencies. Our patients performed worse than controls in both tests (higher C-index and S-

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index, reaching ranges similar to protanomalies) although these differences did not reach statistical significance as established by Bonferroni correction. L'Anthony S-index p value was <0.05, indicating that our patients had a (subtle) tendency to protanomaly (S-index of 1.95). In this study only one eye was tested per person. Some recent studies suggest asymmetrical involvement of the retina in PD and accept the incorporation of both eyes of each patient in the study.[21] Thus, the diagnostic yield in this study may have been lowered by including a potentially lesser affected eye. However, incorporating both eyes of a patient may sometimes be controversial: a minimum symmetric structural and functional alterations could have been masked and generated a % of dependence between measurements. The majority of authors consider the inclusion of only one eye of each patient adequate for statistical analysis because RNFL measurements correlate significantly between the two eyes; therefore, we included only one eye per patient. Previous studies have indicated that PD patients lose foveal contrast sensitivity to patterns to

which normal observers are most sensitive (i.e., requiring the least contrast for detection).[8,9] Ganglion cells in the retina show adaptation to visual contrast and pool visual inputs over their receptive fields through an array of parallel bipolar cells with smaller receptive fields.[22] The parvo- and magnocellular ganglion cells are located in the RGC layer and take two different pathways for the identification of color and contrast at different frequencies.[23] RGC loss (as observed using SD-OCT) was recently identified as the cause of visual impairment in patients suffering from another neurodegenerative process, multiple sclerosis.[24] Thus, a similar process could be the cause of the contrast and color deficiencies in patients with PD. In addition, in the mammalian retina, color vision and contrast sensitivity are modulated through D1 and D2 receptors. These dopaminergic receptors are differentially located in the retinal layers and a

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complete lack of activation leads to signal dispersion and alterations in color vision and contrast sensitivity.[2] Alteration of the retinal layers in PD was first demonstrated in 2004.[25] Since then, various studies have demonstrated different results.[3-5,25-28] Previous studies performed by our team confirmed that both macular thickness and the RNFL were affected in patients with PD, especially in the inferior and temporal quadrants.[4,5, 29] Moreover, Garcia-Martin et al demonstrated that the inner retinal layers were most affected in these patients, and that the GCL thickness was inversely correlated with disease duration and PD severity, and was predictive of axonal damage in these patients.[30] The present study included a smaller number of patients, which may have affected the significance of our results compared to previous studies. We could only detect a significant reduction in the minimum GCL+IPL thickness in PD patients compared to healthy subjects, after correction for multiple comparisons (using Bonferroni test). However, we detected a clear tendency towards a reduction in the macular, RNFL, and GCL thicknesses (p<0.05). A significant reduction in the temporal sectors of the peripapillary RNFL thickness has been repeatedly observed by different groups [31, 32] and was confirmed in the present study. Two recent studies, however, detected no differences in the peripapillary RNFL thickness of PD patients compared to healthy controls using SD-OCT [27,28] and one study only found significant differences in the nasal quadrant.[33] More studies are required to clarify these contradictory observations. In a previous study, we demonstrated that the retinal thickness corresponding to the papillomacular bundle (as measured with the Axonal Analytics software for Spectralis OCT) correlated (r>0.70) with some functional parameters (such as the mean defect and the pattern

standard deviation of the automated perimetry) in patients with PD.[34] The GCL was not

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investigated at that time, however, and visual function parameters were reduced to perimetry and
color vision measured with the Ishihara color test. The current study evaluated not only the
RNFL but also the GCL thickness, and more visual function parameters were analyzed. The
GCL correlated most with the visual function parameters: GCL thickness was directly associated
with VA and CSV measured at all different spatial frequencies, and inversely correlated with the
color vision indexes. Thus, GCL thinning is linked to color deficiencies, contrast sensitivity loss,
and lower vision at different contrast levels in PD patients.

The degree of correlation is usually classified as low (<0.30), moderate (0.30–0.70), or strong (>0.70). Our results revealed a low and moderate degree of correlation between most parameters, consistent with findings in other neurodegenerative diseases.[35] Macular thickness and macular volume, however, were strongly associated with functional parameters (VA, CS, and L'Anthony CCI, C-index, and S-index). This strong association, to the best of our knowledge, has not been previously demonstrated in PD.

There are very few studies of the correlation between functional and structural parameters in PD patients. Adam et al [14] demonstrated a significant reduction in the inner retinal layer complex (RNFL + GCL + IPL) in PD patients, but no association with contrast sensitivity (measured with the Pelli Robson chart). A very recent study by Kaur et al [15] demonstrated a correlation between functional parameters and GCL thinning, consistent with our results. Kaur et al, however, found no significant alterations in VA or color vision in PD patients and the severity of the disease was not correlated with structural parameters, in contrast to other studies that demonstrate an association between macular and GCL thickness and disease duration and severity.[29,30] Although the severity of the disease in our sample (based on the Hoehn Yahr scale) was similar to that in Kaur's study, the duration of the disease in our study was higher than

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333	that in Kaur's patients (13 years vs 5 years), which may account for some of the differences in
334	the results between the two studies. These discrepancies (and similarities) support the need for
335	more studies on this topic. Our results, together with previously published studies,[15, 30]
336	suggest that the GCL could be a reliable indicator of structural alterations in the retina of PD
337	patients, demonstrating a significant correlation with functional tests in these patients. The
338	results of the present study have important implications for clinical diagnosis and functional
339	deficits in patients with PD, and highlight the importance of visual function tests in the
340	evaluation of these patients.
341	In conclusion, visual dysfunction was significantly correlated with morphologic parameters in
342	PD patients. PD patients present with a reduction in macular, RNFL, and GCL thickness, with
343	changes in the GCL being most closely associated with visual dysfunction.
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345	Contributorship:
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345 346 347	Contributorship: V. Polo: Research project: organization. Statistical analysis and Manuscript: Review and critique.
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40	369	not-for-profit sectors.	
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42	370	The authors disclose no conflict of interest.	
43 11			
45	371	Data sharing	
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8 9 10 11 12 13 14 15 16	458	Legends	
	459	Figure 1: Correlation between the average macular thickness and contrast sensitivity vision as	
	460	measured with the CSV 1000E test, at a spatial frequency of 6 cycles per degree, in patients with	
	461	Parkinson's disease.	
17 18	462		
19 20	463	Figure 2: Correlation between the average macular thickness and visual acuity as measured with	
21 22	464	ETDRS optotype at a contrast level of 100% in patients with Parkinson's disease.	
23 24 25	465		
25 26 27 28 29	466	Figure 3: Correlation between macular volume and visual acuity as measured with ETDRS	
	467	optotype at a contrast level of 100% in patients with Parkinson's disease.	
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32 33	469	Table 1: Epidemiologic and disease characteristics of patients with PD and healthy subjects, and	
34 35	470	statistical significance (P). Abbreviations: SD, standard deviation; UPDRS III, Unified Parkinson	
36 37	471	Disease Rating Scale part III.	
38 39 40	472		
40 41 42	473	Table 2: Mean and standard deviation (SD) of visual functional parameters in healthy controls	
43	474	and subjects with Parkinson disease. Results in <b>bold letters indicate statistical significance</b>	
44 45 40	475	(p<0.05). The asterisk indicates those values with statistical significance after Bonferroni	
46 47	476	correction for multiple tests (p<0.0125 for VA ETDRS 100, 2.50 and 1.25; p<0.0125 for Pelli	
48 49	477	Robson and CSV 1000E measurements; p<0.0083 for Farnsworth and L'Anthony tests). Bold	
50 51	478	letters indicate parameters with p value <0.05. Abbreviations: VA, visual acuity; ETDRS, early	
52 53	479	treatment diabetic retinopathy study; cpd, cycles per degree; AC CCI, age corrected color	
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confusion index; CCI, color confusion index; C-index, confusion index; Conf Angle, confusion angle; S-index, scatter index; PD, Parkinson disease.

Table 3: Mean and standard deviation (SD) of structural parameters (retinal nerve fiber layer, ganglion cell layer and macular thicknesses) obtained with the Cirrus HD optical coherence tomography device in healthy controls and subjects with Parkinson disease. Bold letters indicate statistical significance (p<0.05). The asterisk indicates those values with statistical significance after Bonferroni correction for multiple tests (p<0.0055 for macular measurements; p<0.0062 for ganglion cell measurements and p<0.01 for RNFL measurements). Bold letters indicate parameters with p value <0.05, Abbreviations: IPL, inner plexiform layer; GCL, ganglion cell layer; RNFL, retinal nerve fiber layer; HD, high definition. 

Table 4: Correlation between macular and ganglion cell layer structural measurements and color vision evaluated with L'Anthony color test in patients with Parkinson disease. Data in bold type correspond to statistically significant correlations (p value <0.05). Abbreviations: GCL, ganglion cell layer; IPL, inner plexiform layer; C-index, Confusion index; CCI, color confusion index; S-index, Scatter index.

Table 5: Correlation between visual acuity measured with ETDRS chart at different levels of contrast (in %) and macular structural measurements (thickness and volume) in patients with Parkinson disease. Correlation data in bold type are statistically significant (p value <0.05). Abbreviations: VA, visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

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Figure 1: Correlation between the average macular thickness and contrast sensitivity vision as measured with the CSV 1000E test, at a spatial frequency of 6 cycles per degree, in patients with Parkinson's disease.  $108 \times 83 \text{mm}$  (300 x 300 DPI)

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Figure 3: Correlation between macular volume and visual acuity as measured with ETDRS optotype at a contrast level of 100% in patients with Parkinson's disease. 119x102mm (300 x 300 DPI)

STROBE Statement-	-Cnecklist of items that should be included in reports of <i>case-control studies</i>					
	Item No	Recommendation				
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstrac				
		Check. This included in the abstract, methods, line 1				
		(b) Provide in the abstract an informative and balanced summary of what was done				
		and what was found				
		Check. This is included in the abstract. Methods, from line 2 to results section line				
Introduction						
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported				
		Check. This is included in the introduction. Paragraph 2.				
Objectives	3	State specific objectives, including any prespecified hypotheses Check. This is				
		included in the introduction. Paragraph 3.				
Methods						
Study design	4	Present key elements of study design early in the paper				
		Check. This is included in Methods, paragraph 1-3.				
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment				
		exposure, follow-up, and data collection				
		Check. This is included in Methods, paragraph 1-3.				
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment				
		and control selection. Give the rationale for the choice of cases and controls				
		Check. This is included in Methods, paragraph 2				
		(b) For matched studies, give matching criteria and the number of controls per case				
		Check. This is included in Methods, paragraph 1				
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect				
		modifiers. Give diagnostic criteria, if applicable				
		Check. Outcomes and variables are explained in Methods, paragraphs 4-8				
Data sources/	8*	For each variable of interest, give sources of data and details of methods of				
measurement		assessment (measurement). Describe comparability of assessment methods if there				
		more than one group				
		Check. Details of measurements are included in paragraphs 4-8.				
Bias	9	Describe any efforts to address potential sources of bias				
		Check. This is included in paragraph 8, line 3-4.				
Study size	10	Explain how the study size was arrived at				
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,				
		describe which groupings were chosen and why				
		Check. Quantitative variables are explained in Methods, paragraphs 4-8				
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding				
		Check. This is included in methods, paragraph 9				
		(b) Describe any methods used to examine subgroups and interactions. Not				
		applicable.				
		(c) Explain how missing data were addressed Not applicable				
		(d) If applicable, explain how matching of cases and controls was addressed Not				
		applicable				
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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially
		eligible, examined for eligibility, confirmed eligible, included in the study,
		completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
		This is a cross sectional study. Inclusion criteria were explained in methods. All
		elegible subjects were included in the study (37) as already explained, all completed
		the evaluation.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and
		information on exposures and potential confounders Check. This is included in
		Results, paragraph 1-2 and table 1.
		(b) Indicate number of participants with missing data for each variable of interest
		Not applicable.
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure
		Check. Numbers and results of each variable are included in results.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and
		their precision (eg, 95% confidence interval). Make clear which confounders were
		adjusted for and why they were included
		Check. Main results include statistical results prior and post multiple comparisons
		adjustment.
		(b) Report category boundaries when continuous variables were categorized Check.
		Category of correlation is explained in discussion, paragraph 5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a
		meaningful time period Not applicable

Other analyses	17	Report other analyses done-eq analyses of subgroups and interactions, and sensitivity analyses
Other analyses	1/	Net analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
		Not applicable
Discussion		
Key results	18	Summarise key results with reference to study objectives Check. This is included in results,
		paragraph 1.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.
		Discuss both direction and magnitude of any potential bias
		Check, this is mentioned in paragraph 3 and 6.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity
		of analyses, results from similar studies, and other relevant evidence
		Check. This is included and discussed along the discussion section.
Generalisability	21	Discuss the generalisability (external validity) of the study results Check. This is included and
		discussed along the discussion section
Other informati	on	
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable,
		for the original study on which the present article is based Check. Not applicable.

\*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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## **BMJ Open**

### Visual dysfunction and its correlation with retinal changes in patients with Parkinson's disease: an observational cross-sectional study

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1 2		
3 4	1	Visual dysfunction and its correlation with retinal changes in patients
5 6	2	with Parkinson's disease: an observational cross-sectional study
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39 40 41	15 16	RUNNING TITLE: OCT and visual dysfunction in Parkinson disease.
42 43	17	STUDY DESIGN AND SETTING: An observational cross-sectional study, carried out at Miguel
44 45	18	Servet University Hospital, in Zaragoza, Spain.
46 47 48	19	KEY WORDS: Parkinson disease, visual function, contrast sensitivity, ganglion cell layer.
49 50	20	WORD COUNT: 2500 words.
51 52	21	All subjects provided detailed consent to participate in this study, which was conducted in
53 54	22	accordance with the guidelines established by the Ethics Committee of the Miguel Servet
55	23	Hospital and based on the principles of the Declaration of Helsinki.
56 57	24	This research received no specific grant from any funding agency in the public, commercial or
58 59 60	25	not-for-profit sectors.

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4 5 6 7 8 9 10 1 12 3 4 5 6 7 8 9 10 1 12 3 4 5 6 7 8 9 00 1 2 2 3 4 5 6 7 8 9 00 1 2 2 3 4 5 6 7 8 9 00 1 2 2 3 4 5 6 7 8 9 00 1 2 3 3 3 3 3 3 3 3 3 3 3 4 4 4 4 4 4 4 4	27	For peer review only - http://bmjopen.bmj.con/site/about/guidelines.xhtml

1 2 3 4 5	28 29	SUBTITLE: Visual acuity, contrast sensitivity vision and color vision are affected in Parkinson disease. Visual dysfunction in these patients correlates with structural changes in the retina
6 7	30	measured with Spectral domain OCT.
8 9	31	
10 11	32 33	
11 12 13 14 56 78 90 12 23 22 22 22 22 22 22 22 22 22 22 22 22	33	

# 34 <u>Abstract</u>

Objectives: To evaluate visual dysfunction and its correlation with structural changes in the
retina in patients with Parkinson disease (PD).

37 Methods: Patients with PD (n=37) and controls (n=37) were included in an observational cross-

38 sectional study and underwent visual acuity (VA), color vision (using the Farnsworth and

39 L'Anthony desaturated D15 color tests), and contrast sensitivity vision (CSV; using the Pelli

40 Robson chart and CSV 1000E test) evaluation to measure visual dysfunction. Structural

41 measurements of the retinal nerve fiber layer (RNFL), and macular and ganglion cell layer

42 (GCL) thicknesses were obtained using spectral domain optical coherence tomography (SD-

43 OCT). Comparison of obtained data and correlation analysis between functional and structural

44 results were performed.

**Results:** VA (in all different contrast levels) and all CSV spatial frequencies were significantly

46 worse in PD patients than in controls. Color vision was significantly affected based on the

47 L'Anthony color test. Significant GCL loss was observed in the minimum GCL + inner

48 plexiform layer. A clear tendency towards a reduction in several macular sectors (central, outer

49 inferior, outer temporal and superior [inner and outer]) and in the temporal quadrant of the

50 RNFL thickness was observed, although the difference was not significant. CSV was the

51 functional parameter most strongly correlated with structural measurements in PD. Color vision

52 was associated with most GCL measurements. Macular thickness was strongly correlated with 53 macular volume and functional parameters (r > 0.70, p < 0.05).

54 Conclusions: Patients with PD had visual dysfunction that correlated with structural changes
55 evaluated by SD-OCT. GCL measurements may be reliable indicators of visual impairment in
56 PD patients.

1 2		
2 3 4	59	Strengths and limitations of this study:
5 6	60	
7 8 9	61	The strengths of this study should be resumed by the following bullet points:
10 11 12	62	- This study includes a complete assessment of visual function parameters and the
12 13 14	63	evaluation of different retinal structures using Spectral domain Optical coherence
15 16	64	tomography in patients with Parkinson disease.
17 18 19	65	- There are only 2 other published articles evaluating the association between visual
20 21	66	dysfunction and morphologic parameters. Results provided by these previous studies
22 23	67	differ from our results, possibly due to different measurement methods and sample size.
24 25 26	68	- Color vision in our study was assessed by L'Anthony and Farnsworth D15 color tests,
27 28	69	which may provide more specific information about color deficiencies. These tests are
29 30 21	70	not commonly used to evaluate color deficiencies in PD patients.
32 33	71	- As an important limitation to our study, we included one randomly selected eye per
34 35	72	patient. The incorporation of both eyes of each patient in Parkinson disease studies is
36 37 38	73	usually recommended due to asymmetrical involvement of the retina in this process.
39 40	74	
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75	
76	Introduction
77	Foveal vision alterations are associated with Parkinson disease (PD), and seem to be caused by
78	dysfunction of the intraretinal dopaminergic circuitry and final retinal output to the brain.[1]
79	Recent studies demonstrated retinal thinning in PD patients compared with healthy subjects.[2-5]
80	Several studies report a correlation between functional disability and axonal loss observed in the
81	optic nerve in multiple sclerosis, another neurodegenerative process.[6,7] PD patients are also
82	reported to have decreased contrast sensitivity and color vision, and altered visual evoked
83	potentials.[1,8-13] To our knowledge, however, very few studies have assessed visual
84	dysfunction in PD and its correlation with morphologic parameters.[14,15]
85	In the present study, we evaluated visual acuity (VA) using an Early Treatment Diabetic
86	Retinopathy Study (ETDRS) chart, contrast sensitivity vision (CSV) using the CSV-1000E test
87	and Pelli-Robson chart, and color vision using the Farnsworth and L'Anthony tests in PD
88	patients and healthy controls to examine the association between visual dysfunction and
89	morphologic parameters.
90	
91	Material and methods
92	Thirty-seven eyes of 37 patients with definite PD and 37 eyes of 37 age- and sex-matched
93	healthy individuals were recruited for an observational cross-sectional study. The study was
94	performed at Miguel Servet University Hospital in Zaragoza, Spain, and all evaluations were
95	performed in one single visit. All procedures adhered to the tenets of the Declaration of Helsinki,

and all participants provided informed consent to participate in the study.

The diagnosis of PD was based on standard clinical and neuroimaging criteria.[16] Information about disease severity was assessed using the Hoehn Yahr scale [17] and the Unified Parkinson Disease Rating Scale part III score (UPDRS III) [18]. Disease duration and treatment were recorded. Exclusion criteria were the presence of significant refractive errors (>5 diopters of spherical equivalent refraction or 3 diopters of astigmatism); intraocular pressure  $\geq 21$  mmHg; media opacifications; concomitant ocular diseases, including history of glaucoma or retinal pathology; and systemic conditions that could affect the visual system. The healthy controls had no history and no evidence of ocular or neurologic disease of any nature; their best-corrected visual acuity (BCVA) was >20/30 based on the Snellen scale. All subjects underwent a complete neuro-ophthalmic evaluation that included pupillary, anterior segment, and funduscopic examination. Visual function was assessed by evaluating BCVA using an ETDRS chart, CSV using the CVS-1000E test and Pelli-Robson chart, and color vision using the Farnsworth desaturated D15 and L'Anthony desaturated D15 tests. Structural analysis of the retina was performed using Spectral domain (SD) optical coherence tomography (OCT) with the Cirrus High definition (HD) OCT (Carl Zeiss Meditec Inc, Dublin, CA), which included three different protocols: macular protocol (for macular thickness analysis), RNFL protocol, and ganglion cell protocol (for individual analysis of this layer). LogMAR visual acuity (VA) was evaluated at three different contrast levels: 100% (HCVA, using ETDRS chart), 2.50%, and 1.25% (LCVA, using Low-Contrast Sloan Letter Charts -Precision Vision, LaSalle, IL-), The percentage indicating the level of contrast, i.e., 100% representing black letters over white background and 1.25% light grey letters over white background. All measurements were obtained under monocular vision and controlled lighting conditions with best correction.

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Contrast sensitivity provides more complete information about visual function than visual acuity tests. CSV was evaluated in our patients using the Pelli-Robson chart and the CVS-1000E test. The Pelli-Robson chart comprises horizontal lines of capital letters organized into groups of three (triplets) with two triplets per line. Within each triplet, all letters have the same contrast. The contrast decreases from one triplet to the next, even within each line. All patients were evaluated under both monocular and binocular vision at a distance of 1 meter from the chart and under controlled fotopic conditions (85  $cd/m^2$ ). The score corresponding to the last triplet of letters seen by the patient was recorded. The CSV-1000E instrument is used worldwide for standardized CSV and glare testing. All patients were evaluated at a distance of 2.5 meters from the chart under monocular vision at 4 different spatial frequencies (3, 6, 12, and 18 cycles per degree [cpd]). The chart comprises four rows with 17 circular patches each. The patches present a grating that decreases in contrast moving from left to right across the row. The patient indicates whether the grating appears in the top patch or the bottom patch for each column. Each contrast value for each spatial frequency was transformed into a logarithmic scale according to standardized values. Color vision was assessed using the Color Vision Recorder (CVR) program. CVR software analyzes chromatic discrimination by classification of colors. The program includes the classic test of Farnsworth 100-hue (FM-100), Farnsworth - Munsell D15, and L'Anthony D15. All patients in the study were evaluated using the Farnsworth - Munsell D15 and L'Anthony D15 protocols and different output parameters such as the Confusion Index (C-index), the Color Confusion Index (CCI), the Confusion angle (Conf Ang), and the Scatter Index (S-index) were recorded.[19,20] The tests were performed under monocular vision. 

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Structural measurements of the retina were obtained using the Cirrus OCT device. The same experienced operator performed all scans and did not apply manual correction to the OCT output. We used an internal fixation target because it provides the highest reproducibility and rejected poor quality scans prior to data analysis. The Cirrus OCT macular cube 512 x 128 protocol provides a macular volume measure and retinal thickness values for nine areas. These areas include a central 1-mm circle representing the fovea, and inner and outer rings measuring 3 mm and 6 mm in diameter, respectively. The inner and outer rings are divided into four quadrants each. The Cirrus OCT optic disc protocol generates images with 200 linear scans enabling analysis of the RNFL of a 6-mm<sup>3</sup> area around the optic nerve. For each scan series of RNFL measurements, we assessed the average, superior, inferior, temporal, and nasal thickness. Cirrus segmentation analysis for retinal layers also provides measurements of the GCL thickness, evaluating six areas of the macular cube (superior, superonasal, inferonasal, inferior, inferotemporal, and superotemporal sectors) and measurements of the average and minimum GCL plus the inner plexiform layer (GCL + IPL) value of a set of 360 spokes, where each average represents the mean number of the pixels along that spoke that lies within the measurement annulus. The minimum is selected because the thinnest portion of the GCL + IPL in the perifoveal region is considered to indicate damage to the ganglion cells. All data analyses were performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL). Due to the parametric distribution of the data, differences between evaluations of PD patients and healthy subjects were compared using Student's t-test. To avoid a high false positive rate, the Bonferroni correction for multiple comparisons was calculated. The level of significance for each variable was established based on Bonferroni calculations. 

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The linear correlation between structural and functional parameters was determined using Pearson's correlation coefficient. Values of p < 0.05 were considered to indicate a significant correlation. Each eye was considered separately, and one eye from each patient was randomly selected for analysis. 

**Results** 

Thirty-seven patients with PD and 37 healthy controls were included in the study. The mean age of the patients with PD was 69 years (range: 58–74 years) and the mean age of the healthy controls was 68 years (range: 60–76 years). Age (p=0.361), sex (p=0.441), and intraocular pressure (p=0.720) did not differ significantly between healthy controls and patients with PD. Mean time from diagnosis of PD was 13.2 years. The median Hoehn Yahr stage was 2.7, and the stage of PD based on the UPDRS III was 25.06 (range: 7-39; Table 1).

Treatment was divided into three different categories: "Drugs that enhance dopamine levels" (carbidopa, levodopa and rasagiline), "dopaminergic drugs" (pramipexole, ropirinol, rotigotine), and "other" (amitriptiline, propranolol, clonazepam). "Drugs that enhance dopamine levels" was the most prescribed category (89% of patients) and combination therapy with levodopa and carbidopa was the most frequent treatment (44%). Sixty-four percent of treatments were categorized as "dopaminergic", most of which were used in combination with drugs included in the previous category. A small percentage of patients (9%) were prescribed drugs with no dopaminergic effects. 

PARAMETER	CONTROLS	PARKINSON DISEASE	р
umber of eyes (n)	37	37	-
Age, years, range	68 (60–76)	69 (58–74)	0.361
Men:Women (% of men)	24:13 (64.9)	23:14 (62.2)	0.441
ntraocular Pressure	15.58 (2.71)	15.12 (2.98)	0.720
visease duration, years, iean (SD)	-	13.2 (5.77)	-
loehn Yahr, mean (SD)	-	2.7 (0.64)	-
PDRS III, mean (SD)	0-	25.06 (8.24)	-
unctional parameters			
<i>unctional parameters</i> D patients had a lower BC	VA at all three c	contrast levels of the ETDR	S chart co
<i>functional parameters</i> D patients had a lower BC ontrols (0.18±0.26 in patie	VA at all three c nts vs -0.065 $\pm$ 0	contrast levels of the ETDR 0.9 in controls at 100%, p=0	S chart co 0.001; 0.5
<i>Sunctional parameters</i> D patients had a lower BC ontrols (0.18±0.26 in patie .44±0.13 at 2.50%, p=0.01	VA at all three c nts vs -0.065 ± 0 0; and 0.61±0.23	contrast levels of the ETDR 0.9 in controls at 100%, p=0 3 vs 0.58±0.16 at 1.25%, p=	S chart co 0.001; 0.5 =0.009). C
<i>Functional parameters</i> D patients had a lower BC ontrols (0.18±0.26 in patie .44±0.13 at 2.50%, p=0.01 ffected in patients at all for	VA at all three c nts vs -0.065 $\pm$ 0 0; and 0.61 $\pm$ 0.23 ur spatial frequer	contrast levels of the ETDR 0.9 in controls at 100%, p=0 3 vs 0.58±0.16 at 1.25%, p= ncies of the CSV 1000E cha	S chart co 0.001; 0.5 =0.009). C art (3, 6, 1
<i>Functional parameters</i> D patients had a lower BC ontrols (0.18±0.26 in patie .44±0.13 at 2.50%, p=0.01 ffected in patients at all for /hen analyzed based on the	EVA at all three c nts vs -0.065 $\pm$ 0 0; and 0.61 $\pm$ 0.22 ur spatial frequer e number of corre	contrast levels of the ETDR 0.9 in controls at 100%, p=0 3 vs 0.58±0.16 at 1.25%, p= ncies of the CSV 1000E cha ect localized gratings (p=0.0	S chart co 0.001; 0.5 =0.009). C art (3, 6, 1 001, <0.0
Functional parameters PD patients had a lower BC controls (0.18±0.26 in patie 0.44±0.13 at 2.50%, p=0.01 ffected in patients at all for when analyzed based on the 0.004 respectively). The Pet	VA at all three c nts vs -0.065 ± 0 0; and 0.61±0.23 ur spatial frequer e number of corre lli Robson result	contrast levels of the ETDR 0.9 in controls at 100%, p=0 3 vs 0.58±0.16 at 1.25%, p= ncies of the CSV 1000E cha ect localized gratings (p=0.0 s also revealed a significant	S chart co 0.001; 0.5 =0.009). C art (3, 6, 1 001, <0.0 : reductio
<i>Functional parameters</i> <sup>1</sup> D patients had a lower BC ontrols (0.18±0.26 in patie .44±0.13 at 2.50%, p=0.01 ffected in patients at all for /hen analyzed based on the .004 respectively). The Pet atients (1.71 in patients vs	VA at all three c nts vs -0.065 $\pm$ 0 0; and 0.61 $\pm$ 0.2 ur spatial frequer e number of corre lli Robson result 1.89 in controls,	contrast levels of the ETDR 0.9 in controls at 100%, p=0 3 vs 0.58±0.16 at 1.25%, p= ncies of the CSV 1000E cha ect localized gratings (p=0.0 s also revealed a significant , p=0.02). Color vision (Cor	S chart co 0.001; 0.5 =0.009). C art (3, 6, 1 001, <0.0 : reductio nf Angle :
<i>Functional parameters</i> D patients had a lower BC ontrols (0.18±0.26 in patie .44±0.13 at 2.50%, p=0.01 ffected in patients at all for /hen analyzed based on the .004 respectively). The Pet atients (1.71 in patients vs est) was also affected in PI	VA at all three c nts vs -0.065 ± 0 0; and 0.61±0.22 ur spatial frequer e number of corre lli Robson result 1.89 in controls, D. The results are	contrast levels of the ETDR 0.9 in controls at 100%, p=0 3 vs $0.58\pm0.16$ at $1.25\%$ , p= ncies of the CSV 1000E cha ect localized gratings (p=0.0 s also revealed a significant , p=0.02). Color vision (Cor e shown in Table 2.	S chart co 0.001; 0.5 =0.009). C art (3, 6, 1 001, <0.0 : reductio nf Angle :
unctional parameters D patients had a lower BC ontrols (0.18±0.26 in patie 44±0.13 at 2.50%, p=0.01 fected in patients at all for hen analyzed based on the 004 respectively). The Pet atients (1.71 in patients vs st) was also affected in PI	VA at all three c nts vs -0.065 ± 0 0; and 0.61±0.22 ur spatial frequer e number of corre lli Robson result 1.89 in controls, D. The results are	contrast levels of the ETDR: 0.9 in controls at 100%, p=0 3 vs $0.58\pm0.16$ at $1.25\%$ , p= ncies of the CSV 1000E cha ect localized gratings (p=0.0 s also revealed a significant , p=0.02). Color vision (Cor e shown in Table 2.	S chart co 0.001; 0.5 =0.009). C art (3, 6, 1 001, <0.0 : reduction of Angle :

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	HEALTHY	HEALTHY CONTROLS		N DISEASE ENTS	SIGNIFICANCE
	Mean	SD	Mean	SD	(P)
VA ETDRS 100	-0.06	0.096	0.18	0.26	0.001*
VA ETDRS 2.5	0.44	0.13	0.59	0.22	0.010*
VA ETDRS 1.25	0.58	0.16	0.62	0.23	0.009*
Pelli Robson	1.89	0.11	1.71	0.17	0.002*
CSV 1000 3 cpd	1.72	0.16	1.49	0.35	0.001*
CSV 1000 6 cpd	1.94	0.13	1.62	0.34	<0.001*
CSV 1000 12 cpd	1.62	0.17	1.26	0.41	<0.001*
CSV 1000 18 cpd	1.11	0.22	0.73	0.34	0.004*
Farnsworth AC CCI	1.11	0.22	0.73	0.34	0.851
Farnsworth C- index	1.10	0.20	1.24	0.42	0.093
Farnsworth CCI	1.07	0.12	1.14	0.24	0.110
Farnsworth Conf Angle	63.90	11.15	65.84	7.49	0.392
Farnsworth S-index	1.56	0.22	1.64	0.39	0.278
Farnsworth time	78.67	28.96	82.91	33.10	0.616
L'Anthony AC CCI	1.05	0.19	1.02	0.18	0.489
L' Anthony C-index	1.43	0.39	1.64	0.53	0.058
L' Anthony CCI	1.30	0.23	1.44	0.37	0.066
L' Anthony Conf Angle	62.31	14.74	71.91	9.25	0.002*
L' Anthony S-index	1.69	0.43	1.95	0.48	0.020
L' Anthony time	77.14	25.99	84.09	39.31	0.431
0 1 Table 2					
2					
3 Structural parame	ters				

#### Table 2

### Structural parameters

Based on Bonferroni corrections, OCT measurements indicated a significant difference in the minimum GCL+IPL value (80.18±6.19 µm vs 82.45±3.60 µm; p=0.005). However, we observed a clear tendency towards a reduction in superior macular sectors, in the outer inferior, outer temporal, and central macular thickness in PD patients compared to controls: the p value for these variables was <0.05 but did not meet Bonferroni significance (results are shown in Table
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209 2). The segmentation analysis revealed a tendency towards reduced GCL in PD patients in the
210 superior (81.64±7.08 µm in patients vs 84.55±4.32 µm in controls; p=0.032) and superonasal
211 sectors (81.04±7.23 µm vs 85.28±4.78 µm; p=0.029); and the RNFL was reduced in the
212 temporal quadrant in PD patients (Table 3). These parameters however, did not meet the level of
213 significance stablished by Bonferroni correction.

	CONTROLS		PARKINSON DISEASE			
Structural parameters	Mean	SD	Mean	SD	Р	
Macular measurements						
Central macular thickness	254.75	17.903	248.96	17.765	0.028	
Inner superior macular thickness	327.34	13.094	325.73	19.329	0.019	
Inner nasal macular thickness	328.52	13.263	325.45	17.098	0.091	
Inner inferior macular thickness	326.14	13.179	324.82	17.921	0.106	
Inner temporal macular thickness	315.90	13.615	312.82	15.760	0.945	
Outer superior macular thickness	284.76	9.418	279.44	17.981	0.008	
Outer nasal macular thickness	302.41	12.167	299.18	17.064	0.074	
Outer inferior macular thickness	277.79	10.755	273.76	16.798	0.045	
Outer temporal macular thickness	271.52	10.992	266.23	18.987	0.013	
Ganglion cell layer thickness						
Superior	84.55	4.323	81.61	7.087	0.032	
Superonasal	85.28	4.780	81.04	7.234	0.029	
Inferonasal	84.66	5.314	81.82	7.521	0.135	
Inferior	84.34	5.052	81.91	6.252	0.389	
Inferotemporal	85.79	4.003	83.73	4.860	0.233	
Temporal	83.76	3.324	82.27	5.312	0.069	
Average IPL+GCL	84.83	4.071	82.73	6.230	0.095	
Min IPL+ GCL	82.45	3.601	80.18	6.194	0.005	
RNFL thickness						
Average	96.17	6.714	94.88	11.505	0.105	
Superior	117.90	10.965	118.68	16.861	0.115	
Nasal	73.59	12.724	72.40	15.182	0.345	
Inferior	128.14	14.060	123.20	22.907	0.075	
Temporal	64.97	8.218	61.48	10.553	0.027	

## **Table 3**



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216	Correlation between functional and structural parameters
217	CSV was the functional parameter most frequently associated with structural measurements in
218	PD. The Pelli Robson CSV results correlated with GCL thickness in all sectors, although the
219	association was not strong (r < 0.5). The superonasal (r=0.40, p=0.010), inferonasal (r=0.40,
220	p=0.010), inferior (r=0.43, p=0.005), superotemporal sector (r=0.43, p=0.006), and average
221	GCL+IPL (r=0.45, p=0.004) values had the highest correlations. The Pelli Robson results also
222	correlated with the thickness in different sectors of the RNFL (average, superior, and inferior
223	sectors). Measurements with the CSV 1000E at different spatial frequencies correlated
224	significantly with most GCL measurements. The superonasal ( $r= 0.40$ , $p= 0.013$ ) and
225	superotemporal (r= 0.44, p= 0.006) thickness, average GCL +IPL thickness (r= 0.40, p= 0.012),
226	and the minimum GCL + IPL ( $r= 0.40$ , $p=0.011$ ) at a spatial frequency of 6 cpd; and the
227	superotemporal (r= 0.41, p= 0.01) thickness and the minimum GCL + IPL thickness (r= 0.43,
228	p=0.006) at a spatial frequency of 18 cpd had the strongest correlations between CSV 1000E and
229	GCL thickness. Spatial frequencies of 6 cpd and 18 cpd were strongly correlated with average
230	macular thickness (r= 0.79, p= 0.012; r= 0.77, p= 0.016, respectively) and macular volume (r=
231	0.78, p= 0.013; r= 0.78, p= 0.014, respectively, Figure 1).
232	Color vision assessed by the L'Anthony test was also associated with the structural parameters:
233	The C-index and CCI results were significantly correlated with all outer macular parameters and
234	most of the GCL measurements (see Table 4). A significant association between color vision and
235	the RNFL parameters was only found in isolated sectors. (see Table 4).
236	
237	

			L'Anthony	color test		
	C-index	р	CCI	p	S-index	р
Macular thickness		1		1		ַרָּ דָ
Central	-0.019	0.905	-0.059	0.716	-0.017	0.9 <b>6</b>
Inner superior	-0.146	0.369	-0.119	0.463	-0.167	0.3
Inner nasal	-0.055	0.735	-0.044	0.788	-0.040	0.80
Inner inferior	-0.073	0.654	-0.064	0.697	-0.074	0.6
Inner temporal	-0.049	0.764	-0.031	0.850	-0.126	0.4
Outer superior	-0.377	0.017	-0.380	0.015	-0.271	0.09
Outer nasal	-0.341	0.031	-0.323	0.042	-0.310	0.0
Outer inferior	-0.360	0.022	-0.353	0.025	-0.375	0.0
Outer temporal	-0.360	0.023	-0.361	0.022	-0.350	0.02
Macular average	-0.691	0.019	-0.657	0.028	-0.709	0.0
Macular volume	-0.686	0.020	-0.647	0.032	-0.709	0.0
Ganglion cell layer thickness						Fiate
Superior	-0.380	0.015	-0.369	0.019	-0.287	0.02
Superonasal	-0.383	0.015	-0.337	0.033	-0.350	0.0
Inferonasal	-0.338	0.033	-0.313	0.049	-0.268	0.0
Inferior	-0.341	0.031	-0.311	0.051	-0.282	0.0
Inferotemporal	-0.252	0.116	-0.263	0.101	-0.203	0.26
Temporal	-0.403	0.010	-0.437	0.005	-0.314	0.04
Average IPL+ GCL	-0.381	0.015	-0.358	0.023	-0.319	0.0
Minimum IPL+ GCL	-0.338	0.033	-0.326	0.040	-0.290	0.0

#### Table 4

- The strongest correlation was between the average macular thickness and macular volume and
- the L'Anthony CCI, C-index, and S-index results. No significant correlations were found
- between the Farnsworth's test parameters and structural measurements.

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245	The VA ETDRS results correlated strongly with average macular thickness and macular volume
246	(see Table 5, Figures 2 and 3). There were significant but mild associations between the GCL
247	parameters and VA at 100% (superonasal, inferonasal, and average GCL + IPL thickness, r=-
248	0.38, p=0.016; r=-0.35, p=0.016; and r=0.35, p=0.029, respectively) and 2.50% (superonasal
249	sector, r=-0.36, p=0.023).

-0.765	0.006		
	0.000	-0.761	0.007
-0.718	0.013	-0.715	0.013
-0.738	0.010	-0.729	0.011
	-0.718	-0.718 0.013 -0.738 0.010	-0.718 0.013 -0.715 -0.738 0.010 -0.729

#### Table 5

There was a significant correlation between Hoehn Yahr score and VA contrast level 2.50% (r=0.48, p=0.040), and CS measured with CSV 1000 at a space frequency of 12 cpd (r=-0.59, p=0.038). No correlations were detected between structural and disease severity parameters. 

#### Discussion

In the present study, we evaluated the visual function parameters and assessed the association between visual dysfunction and morphologic changes in the retina of 37 patients with PD. Parameters corresponding to VA at different contrast levels, and all CSV tests results were altered in PD patients in comparison with healthy subjects, prior to and after statistical correction for multiple tests. Moreover, contrast sensitivity was the most affected parameter in our study and correlated with most of the structural data. Color vision was measured with two different tests, the Farnsworth and L'Anthony 15 D tests. These tests provide information for 

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differentiating subjects with severe loss of color vision from those with milder color defects or normal color vision, and also can be used to evaluate acquired loss of color vision. In our study, only the L'Anthony Confusion Angle was significantly altered in PD patients. L'Anthony test is less saturated than the Farnsworth color test, thus it is designed to detect more subtle color deficiencies. Our patients performed worse than controls in both tests (higher C-index and S-index, reaching ranges similar to protanomalies) although these differences did not reach statistical significance as established by Bonferroni correction. L'Anthony S-index p value was <0.05, indicating that our patients had a (subtle) tendency to protanomaly (S-index of 1.95). One important limitation of this study is that only one eye was tested per person. Some recent studies suggest asymmetrical involvement of the retina in PD and recommend the incorporation of both eyes of each patient in the study.[21] Thus, the diagnostic yield in this study may have been lowered by including a potentially lesser affected eye. In a similar way, including a randomly selected eye could be innapropiate for other neurological conditions, for example, a tumor compressing one optic nerve. However, incorporating both eyes of a patient may sometimes be controversial since a minimum symmetric structural and functional alterations could have been masked and generated a % of dependence between measurements. Previous studies have indicated that PD patients lose foveal contrast sensitivity to patterns to which normal observers are most sensitive (i.e., requiring the least contrast for detection).[8,9] Ganglion cells in the retina show adaptation to visual contrast and pool visual inputs over their receptive fields through an array of parallel bipolar cells with smaller receptive fields.[22] The parvo- and magnocellular ganglion cells are located in the RGC layer and take two different pathways for the identification of color and contrast at different frequencies.[23] RGC loss (as 

observed using SD-OCT) was recently identified as the cause of visual impairment in patients

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suffering from another neurodegenerative process, multiple sclerosis.[24] Thus, a similar process could be the cause of the contrast and color deficiencies in patients with PD. In addition, in the mammalian retina, color vision and contrast sensitivity are modulated through D1 and D2 receptors. These dopaminergic receptors are differentially located in the retinal layers and a complete lack of activation leads to signal dispersion and alterations in color vision and contrast sensitivity.[2]

Alteration of the retinal layers in PD was first demonstrated in 2004.[25] Since then, various studies have demonstrated different results.[3-5,25-28] Previous studies performed by our team confirmed that both macular thickness and the RNFL were affected in patients with PD, especially in the inferior and temporal quadrants.[4,5, 29] Moreover, Garcia-Martin et al demonstrated that the inner retinal layers were most affected in these patients, and that the GCL thickness was inversely correlated with disease duration and PD severity, and was predictive of axonal damage in these patients. [30] The present study included a smaller number of patients, which may have affected the significance of our results compared to previous studies. We could only detect a significant reduction in the minimum GCL+IPL thickness in PD patients compared to healthy subjects, after correction for multiple comparisons. However, we detected a clear tendency towards a reduction in the macular, RNFL, and GCL thicknesses. A significant reduction in the temporal sectors of the peripapillary RNFL thickness has been repeatedly observed by different groups [31, 32] and this reduction was also observed in the present study. Two recent studies, however, detected no differences in the peripapillary RNFL thickness of PD patients compared to healthy controls using SD-OCT [27,28] and one study only found significant differences in the nasal quadrant.[33] More studies are required to clarify these contradictory observations. 

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In a previous study, we demonstrated that the retinal thickness corresponding to the papillomacular bundle (as measured with the Axonal Analytics software for Spectralis OCT) correlated (r>0.70) with some functional parameters (such as the mean defect and the pattern standard deviation of the automated perimetry) in patients with PD.[34] The GCL was not investigated at that time, however, and visual function parameters were reduced to perimetry and color vision measured with the Ishihara color test. The current study evaluated not only the RNFL but also the GCL thickness, and more visual function parameters were analyzed. The GCL correlated most with the visual function parameters: GCL thickness was directly associated with VA and CSV measured at all different spatial frequencies, and inversely correlated with the color vision indexes. Thus, GCL thinning is linked to color deficiencies, contrast sensitivity loss, and lower vision at different contrast levels in PD patients. The degree of correlation is usually classified as low (<0.30), moderate (0.30-0.70), or strong (>0.70). Our results revealed a low and moderate degree of correlation between most parameters, consistent with findings in other neurodegenerative diseases.[35] Macular thickness and macular 

volume, however, were strongly associated with functional parameters (VA, CS, and L'Anthony
CCI, C-index, and S-index). This strong association, to the best of our knowledge, has not been
previously demonstrated in PD.

There are very few studies of the correlation between functional and structural parameters in PD patients. Adam et al [14] demonstrated a significant reduction in the inner retinal layer complex (RNFL + GCL + IPL) in PD patients, but no association with contrast sensitivity (measured with the Pelli Robson chart). A very recent study by Kaur et al [15] demonstrated a correlation between functional parameters and GCL thinning, consistent with our results. Kaur et al, however, found no significant alterations in VA or color vision in PD patients and the severity of

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333	the disease was not correlated with structural parameters, in contrast to other studies that
334	demonstrate an association between macular and GCL thickness and disease duration and
335	severity.[29,30] Although the severity of the disease in our sample (based on the Hoehn Yahr
336	scale) was similar to that in Kaur's study, the duration of the disease in our study was higher than
337	that in Kaur's patients (13 years vs 5 years), which may account for some of the differences in
338	the results between the two studies. These discrepancies (and similarities) support the need for
339	more studies on this topic. Our results, together with previously published studies,[15, 30]
340	suggest that the GCL could be a reliable indicator of structural alterations in the retina of PD
341	patients, demonstrating a significant correlation with functional tests in these patients. The
342	results of the present study have important implications for clinical diagnosis and functional
343	deficits in patients with PD, and highlight the importance of visual function tests in the
344	evaluation of these patients.
345	In conclusion, visual dysfunction was significantly correlated with morphologic parameters in
346	PD patients. PD patients present with a reduction in GCL thickness, which is closely associated
347	with visual dysfunction.
348	
349	Contributorship:
350	V. Polo: Research project: organization. Statistical analysis and Manuscript: Review and
351	critique.
352	M. Satue: Research project: Conception, design, organization and execution. Statistical analysis:
353	Review and critique. Manuscript: Writing of the first draft, review and critique.
354	MJ Rodrigo: Research project: organization and execution. Statistical analysis: Review and

1 2		
2 3 4	355	critique. Manuscript: Writing of the first draft, review and critique.
5 6 7	356	S. Otin: Research project: organization and execution. Statistical analysis: Review and critique.
7 8 9	357	Manuscript: review and critique.
10 11 12	358	R. Alarcia: Research project: organization and execution. Statistical analysis: Review and
13 14	359	critique. Manuscript: review and critique.
15 16 17	360	MP. Bambo: Research project: execution. Statistical analysis: Review and critique. Manuscript:
18 19 20	361	review and critique.
20 21 22	362	MI. Fuertes: Research project: execution. Statistical analysis: Review and critique. Manuscript:
23 24 25	363	review and critique.
26 27	364	JM. Larrosa: Research project: execution. Statistical analysis: Review and critique. Manuscript:
28 29 30	365	review and critique.
31 32 33	366	LE. Pablo: Research project: execution. Statistical analysis: Review and critique. Manuscript:
34 35	367	review and critique.
36 37 38	368	E. Garcia-Martin: Research project: Conception, design, organization and execution. Statistical
39 40	369	analysis: Design, execution, review and critique. Manuscript: Writing of the first draft, review
41 42 43	370	and critique.
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52 53	374	The authors disclose no conflict of interest.
54 55 56 57 58 59 60	375	Data sharing

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All relevant data are included in this manuscript. No additional data available. 

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2 3 4 5	463	Legends
6 7	464	Figure 1: Correlation between the average macular thickness and contrast sensitivity vision as
8 9	465	measured with the CSV 1000E test, at a spatial frequency of 6 cycles per degree, in patients with
10 11 12	466	Parkinson's disease.
13 14 15	467	
16 17 18	468	Figure 2: Correlation between the average macular thickness and visual acuity as measured with
19 20	469	ETDRS optotype at a contrast level of 100% in patients with Parkinson's disease.
21 22 23 24	470	
24 25 26	471	Figure 3: Correlation between macular volume and visual acuity as measured with ETDRS
27 28	472	optotype at a contrast level of 100% in patients with Parkinson's disease.
29 30 31	473	
32 33 34	474	Table 1: Epidemiologic and disease characteristics of patients with PD and healthy subjects, and
35 36	475	statistical significance (P). Abbreviations: SD, standard deviation; UPDRS III, Unified Parkinson
37 38 39	476	Disease Rating Scale part III.
40 41 42	477	
43 44	478	Table 2: Mean and standard deviation (SD) of visual functional parameters in healthy controls
45 46 47	479	and subjects with Parkinson disease. The asterisk indicates those values with statistical
48 49	480	significance after Bonferroni correction for multiple tests (p<0.0125 for VA ETDRS 100, 2.50
50 51 52	481	and 1.25; p<0.0125 for Pelli Robson and CSV 1000E measurements; p<0.0083 for Farnsworth
52 53 54	482	and L'Anthony tests). Abbreviations: VA, visual acuity; ETDRS, early treatment diabetic
55 56	483	retinopathy study; cpd, cycles per degree; AC CCI, age corrected color confusion index; CCI,
57 58 59 60	484	color confusion index; C-index, confusion index; Conf Angle, confusion angle; S-index, scatter

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index; PD, Parkinson disease.

486	
487	Table 3: Mean and standard deviation (SD) of structural parameters (retinal nerve fiber layer,
488	ganglion cell layer and macular thicknesses) obtained with the Cirrus HD optical coherence
489	tomography device in healthy controls and subjects with Parkinson disease. The asterisk
490	indicates those values with statistical significance after Bonferroni correction for multiple tests
491	(p<0.0055 for macular measurements; p<0.0062 for ganglion cell measurements and p<0.01 for
492	RNFL measurements). Abbreviations: IPL, inner plexiform layer; GCL, ganglion cell layer;
493	RNFL, retinal nerve fiber layer; HD, high definition.
494	
495	Table 4: Correlation between macular and ganglion cell layer structural measurements and color
496	vision evaluated with L'Anthony color test in patients with Parkinson disease. Data in bold type
497	correspond to statistically significant correlations (p value <0.05). Abbreviations: GCL, ganglion
498	cell layer; IPL, inner plexiform layer; C-index, Confusion index; CCI, color confusion index; S-
499	index, Scatter index.
500	
501	Table 5: Correlation between visual acuity measured with ETDRS chart at different levels of
502	contrast (in %) and macular structural measurements (thickness and volume) in patients with
503	Parkinson disease. Correlation data in bold type are statistically significant (p value <0.05).
504	Abbreviations: VA, visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.
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57 58 59				
60		_	 	





Figure 1: Correlation between the average macular thickness and contrast sensitivity vision as measured with the CSV 1000E test, at a spatial frequency of 6 cycles per degree, in patients with Parkinson's disease.  $108 \times 83 \text{mm}$  (300 x 300 DPI)

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Figure 3: Correlation between macular volume and visual acuity as measured with ETDRS optotype at a contrast level of 100% in patients with Parkinson's disease. 119x102mm (300 x 300 DPI)

STROBE Statement-	nt—Checklist of items that should be included in reports of <i>case-control studies</i>				
	Item No	Recommendation			
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstrac			
		Check. This included in the abstract, methods, line 1			
		(b) Provide in the abstract an informative and balanced summary of what was done			
		and what was found			
		Check. This is included in the abstract. Methods, from line 2 to results section line			
Introduction					
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported			
		Check. This is included in the introduction. Paragraph 2.			
Objectives	3	State specific objectives, including any prespecified hypotheses Check. This is			
	Õ	included in the introduction. Paragraph 3.			
Methods					
Study design	4	Present key elements of study design early in the paper			
		Check. This is included in Methods, paragraph 1-3.			
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment			
		exposure, follow-up, and data collection			
		Check. This is included in Methods, paragraph 1-3.			
Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment			
		and control selection. Give the rationale for the choice of cases and controls			
		Check. This is included in Methods, paragraph 2			
		(b) For matched studies, give matching criteria and the number of controls per case			
		Check. This is included in Methods, paragraph 1			
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect			
		modifiers. Give diagnostic criteria, if applicable			
		Check. Outcomes and variables are explained in Methods, paragraphs 4-8			
Data sources/	8*	For each variable of interest, give sources of data and details of methods of			
measurement		assessment (measurement). Describe comparability of assessment methods if there			
		more than one group			
		Check. Details of measurements are included in paragraphs 4-8.			
Bias	9	Describe any efforts to address potential sources of bias			
		Check. This is included in paragraph 8, line 3-4.			
Study size	10	Explain how the study size was arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable,			
		describe which groupings were chosen and why			
		Check. Quantitative variables are explained in Methods, paragraphs 4-8			
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding			
		Check. This is included in methods, paragraph 9			
		(b) Describe any methods used to examine subgroups and interactions. Not			
		applicable.			
		(c) Explain how missing data were addressed Not applicable			
		(d) If applicable, explain how matching of cases and controls was addressed Not			
		applicable			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially
		eligible, examined for eligibility, confirmed eligible, included in the study,
		completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
		This is a cross sectional study. Inclusion criteria were explained in methods. All
		elegible subjects were included in the study (37) as already explained, all completed
		the evaluation.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and
		information on exposures and potential confounders Check. This is included in
		Results, paragraph 1-2 and table 1.
		(b) Indicate number of participants with missing data for each variable of interest
		Not applicable.
Outcome data	15*	Report numbers in each exposure category, or summary measures of exposure
		Check. Numbers and results of each variable are included in results.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and
		their precision (eg, 95% confidence interval). Make clear which confounders were
		adjusted for and why they were included
		Check. Main results include statistical results prior and post multiple comparisons
		adjustment.
		(b) Report category boundaries when continuous variables were categorized Check.
		Category of correlation is explained in discussion, paragraph 5
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a
		meaningful time period Not applicable

Other analyses	17	Report other analyses done-eg analyses of subgroups and interactions, and sensitivity analyses			
		Not applicable			
Discussion					
Key results	18	Summarise key results with reference to study objectives Check. This is included in results,			
		paragraph 1.			
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision.			
		Discuss both direction and magnitude of any potential bias			
		Check, this is mentioned in paragraph 3 and 6.			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity			
		of analyses, results from similar studies, and other relevant evidence			
		Check. This is included and discussed along the discussion section.			
Generalisability	21	Discuss the generalisability (external validity) of the study results Check. This is included and			
		discussed along the discussion section			
Other information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable,			
		for the original study on which the present article is based Check. Not applicable.			

\*Give information separately for cases and controls.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.