Title

Association of Structural and Functional Measures With Contrast Sensitivity in Glaucoma.

Authors

Fatehi, Nima
Nowroozizadeh, Sara
Henry, Sharon
et al.

Publication Date

2017-06-01

DOI

10.1016/j.ajo.2017.03.019

Peer reviewed

HHS Public Access

Author manuscript

Am J Ophthalmol. Author manuscript; available in PMC 2017 October 24.

Published in final edited form as:

Am J Ophthalmol. 2017 June ; 178: 129–139. doi:10.1016/j.ajo.2017.03.019.

Association of Structural and Functional Measures with Contrast Sensitivity in Glaucoma

Nima Fatehi, **Sara Nowroozizadeh**, **Sharon Henry**, **Anne L. Coleman**, **Joseph Caprioli**, and **Kouros Nouri-Mahdavi**

Glaucoma Division, Stein Eye Institute, David Geffen School of Medicine, University of California Los Angeles, Los Angeles

Abstract

PURPOSE—To test the hypothesis that structural and functional measures predict contrast sensitivity (CS) outcomes in glaucomatous eyes.

DESIGN—Cross-sectional prospective study.

METHODS—105 eyes of 65 patients who underwent macular SD-OCT imaging, 24-2 standard achromatic visual fields (VF) and CS measurement on the same day were enrolled. Association of CS at 4 spatial frequencies (3, 6, 12 and 18 cycles per degree, cpd), with structural and functional outcomes was explored with correlation and regression analyses.

RESULTS—The median (IQR) 24-2 visual field mean deviation was −7.6 (−11.1 to −3.0). Significant correlations were found between CS at 6 cpd and ganglion cell/inner plexiform layer thickness at inferotemporal and inferonasal macular sectors (ρ =0.222, p=0.023 and ρ =0.209, p=0.032, respectively). CS at 6 cpd demonstrated higher correlations with full macular thickness measurements, the strongest of which was with the central macular thickness in the superior 6×3 degree region (ρ =0.311, p=0.001). Contrast sensitivity at 6 cpd also had the strongest correlation with mean deviation of the 4 central VF points (ρ=−0.420; p<0.001). There was a significant correlation between logMAR visual acuity and contrast sensitivity at 6, 12, and 18 cpd (ρ = −0.306, −0.348 and −0.241, p<0.013, respectively).

CONCLUSIONS—Structural and functional measures showed a fair relationship with contrast sensitivity. This association was most prominent between full thickness macular measures or central VF parameters and CS at 6 cpd. Contrast sensitivity was not a reliable surrogate for glaucoma severity in this cross-sectional study.

Corresponding author: Kouros Nouri-Mahdavi, MD, MSc, Stein Eye Institute, 100 Stein Plaza, Los Angeles, CA 90095, nouri-mahdavi@jsei.ucla.edu, Phone: 310-794-1487, Fax: 310-794-6616.

Presented as a poster at the annual meeting of the Association for Research in Vision and Ophthalmology, May 5–9, 2014, Orlando FL.

Nima Fatehi: “No financial disclosure”, Sara Nowroozizadeh: “No financial disclosure”, Sharon Henry: “No financial disclosure”, Ann L. Coleman: “Aerie Pharmaceuticals: consultant, Alcon: Consultant”, Joseph Caprioli: “No financial disclosure”, Kouros Nour-Mahdavi: “No financial disclosure”

Introduction

Contrast sensitivity (CS) is an important aspect of human vision and is frequently affected in patients with glaucoma with various degrees of damage.[1–3] Conventional psychophysical measures of visual function such as visual fields reveal the location and extent of the visual defect and allow the clinician to determine the severity or progression of the disease. However, these tests have limited ability to indicate the level of disability experienced by the patient.[3,4] It has been proposed that assessing monocular CS might be more useful in monitoring the progression of functional visual loss than testing visual fields, which is more costly and time-consuming.[5] Subjects with glaucoma can have impaired CS despite good visual acuity.[6–8] Changes in CS of glaucomatous eyes have been detected prior to visible damage to the retinal nerve fiber layer, manifest defects on standard automated perimetry, or a decrease in visual acuity (VA).[3,9,10]

Glaucoma preferentially affects the retinal ganglion cells (RGC) and their neural processes located in the retinal nerve fiber layer (RNFL) and the inner plexiform layer (IPL), which contains the RGC dendrites.[11–15] The inner retinal layers can now be measured with reasonable accuracy with spectral domain optical coherence tomography (SD-OCT). Recent advances in OCT segmentation algorithms have facilitated visualization and measurement of individual retinal layers in the macular region with SD-OCT.[16–23] There is no study, to date, that has addressed the relationship between CS and inner macular measurements in glaucomatous eyes.

The present study was carried out to test the hypothesis that structural and functional measures predict CS outcomes in eyes with glaucoma. In case such associations are strong, measurement of CS could be advocated for monitoring patients with glaucoma, especially those with advanced disease in whom structural and functional tests have limited utility.

Methods

Study sample

Patients from the Advanced Glaucoma Progression Study cohort who met specific inclusion criteria were enrolled in this study. The Institutional Review Board’s approval was obtained and all patients gave their written informed consent. Our study protocol was carried out in accordance with the principles of the Declaration of Helsinki and The Health Insurance Portability and Accountability Act.

All patients had a comprehensive eye exam including visual acuity, automated refraction, measurement of intraocular pressure (IOP), gonioscopy, slit-lamp exam, dilated fundus exam, 24-2 standard achromatic perimetry (SAP), macular SD-OCT imaging with Cirrus and Spectralis devices and CS measurement with the CSV-1000 device.

Glaucoma was defined as presence of glaucomatous optic nerve damage (i.e., vertical cup-to-disc ratio of >0.6, or cup to disc asymmetry >0.2, or presence of focal thinning or notching) and an associated visual field defect on standard achromatic perimetry. A visual field defect was considered to be present if both of the following criteria were met: (1)

Glaucoma Hemifield Test outside normal limits; and (2) four abnormal points with p <5% on the pattern deviation plot, both confirmed at least once. These criteria have been shown to be highly specific and reasonably sensitive for detection of early glaucomatous visual field loss.[24] Patients were required to have a visual field mean deviation (MD) worse than −6 dB or evidence of involvement of two or more points within the central 10 degrees of the 24-2 field (p values <5% on the pattern deviation plot) confirmed at least once.

Other inclusion criteria for the study subjects were age 40–85 years, best corrected visual acuity ≥20/50 in the eligible eye, spherical refractive error ≤5 D and ≤3 D of astigmatism, and no significant retinal or neurological disease including diabetic retinopathy or age-related macular degeneration. Eligible patients could have had prior incisional or laser glaucoma surgery or cataract extraction as long as the above criteria were met.

The CSV-1000 (VectorVision, Grenville, OH) measures contrast sensitivity at 3, 6, 12, and 18 cycles/degree frequencies. The device automatically calibrates the light level to 85 cd/m^2. The patients were examined at a distance of 8 feet from the device's screen. The device projects 4 double rows (rows A, B, C and D) displaying circles of decreasing contrast sensitivity at 3, 6, 12 and 18 cycles/degree, respectively. Each row consists of 17 circles, with the first circle of each row displaying the highest contrast. The remaining 16 circles are presented in 2 rows consisting of 8 pairs of circles. The patient is instructed to choose the one circle out of each pair showing the grid pattern. The last correct response for each level of contrast is defined as the contrast threshold for that spatial frequency.

The Posterior Pole Algorithm of Spectralis® SD-OCT (Heidelberg Engineering, Germany) and the Macular Cube 200 × 200 protocol of Cirrus high-definition OCT (HD-OCT, Model 4000; software version 6.0, Carl Zeiss Meditec Inc., Dublin, CA, USA) were used for macular imaging. The SD-OCT images were performed after dilation. The xml data from both devices were exported to a personal computer and processed. All the images were reviewed by one of the investigators (SN), and images with signal strength <7 (Cirrus HD-OCT) or quality factor <15 (Spectralis SD-OCT), missing data, obvious motion artifact, or incorrect segmentation were excluded. The macular imaging algorithm of the Spectralis SD-OCT (Posterior Pole Algorithm) consists of 61 horizontal B-scans each consisting of 768 A-scans spanning a 30×25° wide area. At each position, acquisition of B-scans is repeated 9–11 times to decrease speckle noise (Automatic Real Time or ART =9–11). The data are then averaged and an 8×8 grid of thickness measurements (64 superpixels within the central 24×24°, each 3° wide) for the full macular thickness is created (see Figure 1). The Macular Cube 200 × 200 algorithm measures 40,000 axial scans (in a 6×6×2 mm cube) centered on the fovea. The ganglion cell analysis available on the Cirrus software version 6.0 (or higher) measures the combined thickness of the ganglion cell and inner plexiform layers (GC/IPL) in a 4.8 × 4.0 mm oval area with a longer horizontal axis (Figure 2). It provides GC/IPL measurements in 6 wedge-shaped sectors after excluding the central foveal region (1.2×1 mm in diameter) along with a pseudocolor scheme for the GC/IPL thickness and a deviation map.[14]

Standard automated perimetry (SAP) 24-2 with Swedish Interactive Thresholding Algorithm was performed for all patients. Visual fields with false negative response rate >33%, false

positive response rate more than 15% and fixation loss rate >20% were excluded. As we expected that CS would be more closely related to central visual function, we defined and calculated the sectoral mean deviation (MD) for the following sectors or regions in addition to the global MD provided by the device (Figure 3): central 4 points, superior paracentral 4 points, inferior paracentral 4 points, central 10-degree visual field (includes 12 test locations in a cross-shaped pattern), superior central 10-degree hemifield, inferior central 10-degree hemifield, inferior 24-2 hemifield and superior 24-2 hemifield. The total deviation values were converted to 1/Lambert units before averaging and then were reconverted back to dB values. Similarly, we defined various regions on the macular 8×8 grids from Spectralis as follows (Figure 1): central 2×2, superior central 2×1, inferior central 2×1, central 4×4, superior central 4×2, inferior central 4×2, central 6×6, superior central 6×3 and inferior central 6×3 sectors.

Statistical methods

The correlation between various global and regional structural (full macular thickness and GC/IPL) or functional outcomes (regional and global MD values) with CS was estimated with Spearman's correlation. We also repeated the same analyses with regression analyses with adjustment for inclusion of both eyes of some patients.

All left eye data were flipped to right eye format. As the current study was considered exploratory and since many of the outcomes of interest were correlated, no correction for p values was deemed appropriate and a p value of <0.05 was considered statistically significant. The Stata software version 12.0 (Stata Corps, College Station TX) was used for all analyses.

Results

One hundred-five eyes of 65 subjects were included in the current study. Table 1 shows the demographic and clinical characteristics of the enrolled subjects. The mean (± SD) age of the patients was 67.6 (± 10.4) years. Forty-four (41.9%) eyes were pseudophakic. The median (interquartile range or IQR) logMAR best corrected visual acuity was 0 (0–0.1). The mean (± SD) contrast sensitivity for 3, 6, 12 and 18 cpd was 1.58 (±0.23), 1.77 (±0.21), 1.41 (±0.28) and 0.97 (±0.26) logarithmic units, respectively. The mean (± SD) central macular thickness for the 6×6 superpixel grid (Spectralis SD-OCT) was 286.9 (± 16.81) μm. The median (IQR) average GC/IPL thickness was 64 (58–70) μm. The median (IQR) 24-2 visual field MD was −7.6 (−11.1 to −3.0) dB. The mean (±SD) intraocular pressure (IOP) at the session where CS was measured was 12.5 (±3.4) mmHg.

The axial length, refractive error and IOP did not demonstrate a significant correlation with CS (p >0.713, >0.133, and >0.194 for all correlations, respectively). There was a significant correlation between logMAR visual acuity and contrast sensitivity at 6, 12, and 18 cpd (ρ = −0.306, p =0.001; ρ =−0.348, p <0.001; and ρ =−0.241, p =0.013, respectively). The correlation between CS at 3 cpd and logMAR visual acuity was not statistically significant (ρ =−0.122; p =0.215).

We estimated the correlation between various global or regional visual field summary indices and the four CS levels (Table 2). It can be observed that CS at all spatial frequencies, especially at 6 and 12 cpd, demonstrated an association with the VF indices particularly with the central indices. The highest correlation was detected between CS at 6 cpd and the central 4-point MD (ρ =0.420; p <0.001) (Figure 4). Overall, the central summary indices showed the highest correlation with CS regardless of the frequency and there was no obvious preference for either superior or inferior central field indices to demonstrate a higher correlation with any CS frequency (Figure 5). Table 3 lists the correlation of various visual field indices with logMAR visual acuity. The central 10-degree MD demonstrated the highest correlation with logMAR visual acuity (ρ =−0.351, p <0.001), followed by central 4 points MD (ρ =−0.329, p =0.001) (Figure 6). We also did the same analysis with the actual sensitivity at each sector (sensitivity in apostilb unit) the results were less significant as expected and the magnitude of the correlation has decreased. Data are shown in table 3. The p values have become larger and the magnitude of the correlation has decreased.

Table 5 describes the GC/IPL thickness measurements and their correlations with CS at 4 measured frequencies. There were only few statistically significant correlations between the CS and GC/IPL sectors. For the CS at 6 cpd, a significant correlation was found with the inferior temporal and inferior nasal macular sectors (ρ =0.222, p =0.023 and ρ =0.209, p =0.032, respectively). The CS at 12 cpd had a statistically significant correlation only with the inferior temporal macular GC/IPL sector (ρ =0.248; p =0.023). None of the other spatial frequencies showed a significant correlation with the GC/IPL thickness measures.

Table 6 shows the correlations between full macular thickness parameters derived from the Spectralis SD-OCT and CS at various frequencies. The CS at 18 cpd did not have a significant correlation with any of the full macular thickness parameters. Other CS parameters demonstrated significant correlations with full macular thickness parameters especially with the central and inferior regions of the macula. The strongest correlation was between the CS at 6 cpd and central 2×2 full macular thickness (ρ =0.311, p =0.001) (Figure 5). The correlations still remained statistically significant after adjusting for inclusion of both eyes of some patients and lens status or IOP with regression analyses regardless of the VF units used.

We also assessed the correlation between logMAR VA and structural measures. We did not find any statistically significant correlation between logMAR VA and any full macular thickness parameters from the Spectralis SD-OCT. LogMAR VA correlated significantly with the inferotemporal GCL/IPL sector thickness (ρ =−0.262, p =0.007).

Discussion

The aim of this study was to test the hypothesis that functional and structural measures predict contrast sensitivity in glaucoma patients. If this hypothesis were proven and the magnitude of such correlations were large enough, CS measurement could be used as an outcome measure for confirming worsening of glaucoma over time. This would be especially useful in eyes with moderate to advanced glaucoma as detection of progression in such eyes is challenging.[25] Some prior studies reported a decrease in CS at 3 and 6 cpd in

glaucoma,[26–28] whereas a few others found a more prominent loss at 6 and 12 cpd.[29,30] Our study confirms the prominent involvement of CS at 6 cpd frequency in glaucoma patients. Contrast sensitivity at 6 cpd was most frequently involved and demonstrated the strongest associations with structural or functional measures.

Our analyses showed fair correlations between contrast sensitivity and VF loss especially in the central region. When VF measures were converted to 1/L units, the correlations became weaker and the p values became larger (i.e., less significant) although the overall trend of correlations was similar. Also, VF correlations with CS were generally larger than those for macular structural measures (highest correlation coefficient of 0.421 compared with 0.311). This was expected since both VF and CS reflect different functional aspects of the human visual system. Wilensky et al. reported an association between decreased contrast sensitivity and worse visual field MD on 24-2 tests.[9] The correlation was stronger among patients with primary open angle glaucoma than patients with ocular hypertension. Tochel et al. explored whether the site of VF loss was associated with decreased CS when the latter was measured in 4 quadrants between 10–20 degrees from fixation.[31] A reduction in CS was in agreement with the location of VF loss only in half of glaucoma patients. They speculated that a decrease in contrast sensitivity represents a different kind of glaucomatous damage, as it was not always related to visual field loss. As mentioned above, in our study, the central visual field sensitivity seemed to be the best predictor of CS loss, especially for spatial frequencies at 6 and 12 cpd. We have to emphasize that the association between contrast sensitivity and various global or regional VF summary indices was modest to fair at best in our study. The average central 4 points had the highest correlation with CS parameters (ρ =0.421).

There are few prior reports in the literature on the potential association of structural measures with CS in glaucoma patients. Agrawal and colleagues found that CS and BCVA were strongly related to macular thickness with Cirrus HD-OCT in patients with primary open angle glaucoma.[32] Because of the redundancy of retinal ganglion cells in the human visual system, visual field damage tends to emerge when at least 25–30% retinal ganglion cells are lost.[33–36] A puzzling finding of our study was that the magnitude of the correlations between GC/IPL thickness measures and CS was not as high as the correlations of the latter with FT thickness measurements. For both macular outcomes, the strongest correlations were observed with CS at 6 cpd. The reason for the stronger correlations observed between CS and FT macular measurements is not immediately apparent but could possibly be attributed, at least partially, to the lower precision in GCIPL measurements as the segmentation of the inner GCL and outer IPL borders is more challenging compared to that of the internal limiting membrane and retinal pigment epithelium for FT parameters. Prior studies exploring utility of macular measurements actually found the GC/IPL layer thickness to perform better for discriminating glaucoma from normal eyes.[37–39] One alternative explanation might be that the outer retinal circuitry may somehow influence CS in glaucoma patients. However, existence of outer retinal damage in glaucoma patients is controversial.[40–42] Although these structural parameters are highly associated with the presence of VF defects,[43,44] based on our findings, they don’t seem to be strong predictors of CS.

Another interesting finding of our study was that the only significant observed correlations with macular GC/IPL measurements were seen in the inferior macula (inferotemporal and inferonasal sectors with CS at 6 and 12 cpd). This raises the question whether specific subsets or regions of retinal ganglion cells determine CS. Alternatively, this could be due to the fact that the inferotemporal GCIPL is the macular sector most commonly affected in early glaucoma[14,45] and therefore, it had a slightly higher range of variation. Whether this inferior localization of macular damage has any pathophysiological significance is not quite clear at this point especially since it was not observed with FT macular measurements.

There was a statistically significant correlation between logMAR VA and CS at 6, 12, and 18 cpd. It has been reported that glaucoma patients with good VA have worse contrast sensitivity compared to normal people.[6] Kim et al. demonstrated a curvilinear correlation between BCVA and SD-OCT parameters and found that BCVA had the highest correlation with the average RNFL thickness ($\rho = -0.447$) compared with regional RNFL and GCC parameters (global, superior and inferior GCC thickness).[46] The VA was related mostly to central VF parameters as expected. Wilensky et al., reported that VA was correlated with the visual field MD deviation ($\rho = -0.193$), but they did not explore other summary indices.[9] Visual acuity was not related to any of the full thickness macular measures; interestingly, the only significant correlation between VA and OCT measures was found with the inferotemporal sectoral thickness.

The results of our study should be interpreted in the light of its potential shortcomings. Our findings likely represent a best-case scenario for the association between CS and structural and functional measures as our study sample was specifically chosen to have at least very early evidence of central field loss and macular damage. However, our patient sample consisted of a group of eyes where severity had a wide range; while the median MD was −7.5, the IQR ranged from −11.1 to −3.0 dB meaning that 25% of our patients had an MD better than −3 dB. Although we could not control for cataract in our study sample, the median VA was 20/20 in this study and 42% of the eyes were already pseudophakic. Our study consisted of a cross-sectional sample of eyes and therefore, inter-individual variability among study eyes may have diluted correlations between structural and functional measures with CS in glaucoma. All the included eyes were under treatment. Given reports on partial reversibility of CS loss in patients after treatment,[47–49] it is not clear how this might have affected the findings.

In summary, we found fair correlations between central VF summary indices and central full macular thickness measurements with CS, most markedly at 6 cpd. Weaker associations were observed between inferior GC/IPL thickness parameters and CS at 6 and 12 cpd. Given our findings, CS outcomes do not seem to be adequate surrogates to be used for detection of disease worsening in glaucoma eyes beyond the very early stages. However, longitudinal studies are needed to better investigate the association of changes in macular structural and functional measures with changes in CS over time in glaucoma. We expect that long-term follow-up of patients enrolled in our study will provide more definitive answers in this regard.

Acknowledgments

This study was supported by an NIH Mentored Patient-oriented Research Career Development Award (5K23EY022659) (KNM) and an unrestricted Departmental Grant from Research To Prevent Blindness.

References

1. Atkin A, Bodis-Wollner I, Wolkstein M, Moss A, Podos SM. Abnormalities of central contrast sensitivity in glaucoma. Am J Ophthalmol. 1979; 88(2):205–211. [PubMed: 474692]
2. Ross JE. Clinical detection of abnormalities in central vision in chronic simple glaucoma using contrast sensitivity. Int Ophthalmol. 1985; 8(3):167–177. [PubMed: 4066159]
3. Ross JE, Bron AJ, Clarke DD. Contrast sensitivity and visual disability in chronic simple glaucoma. Br J Ophthalmol. 1984; 68(11):821–827. [PubMed: 6498136]
4. Cullinan TR. Epidemiology of visual disability. Trans Ophthalmol Soc U K. 1978; 98(2):267–269. [PubMed: 155907]
5. Richman J, Lorenzana LL, Lankaranian D, et al. Importance of visual acuity and contrast sensitivity in patients with glaucoma. Arch Ophthalmol. 2010; 128(12):1576–1582. [PubMed: 21149782]
6. Onal S, Yenice O, Cakir S, Temel A. FACT contrast sensitivity as a diagnostic tool in glaucoma: FACT contrast sensitivity in glaucoma. Int Ophthalmol. 2008; 28(6):407–412. [PubMed: 18000646]
7. Lahav K, Levkovitch-Verbin H, Belkin M, Glovinsky Y, Polat U. Reduced mesopic and photopic foveal contrast sensitivity in glaucoma. Arch Ophthalmol. 2011; 129(1):16–22. [PubMed: 21220624]
8. Stamper RL. Psychophysical changes in glaucoma. Surv Ophthalmol. 1989; 33(Suppl):309–318. [PubMed: 2655144]
9. Wilensky JT, Hawkins A. Comparison of contrast sensitivity, visual acuity, and Humphrey visual field testing in patients with glaucoma. Trans Am Ophthalmol Soc. 2001; 99:213–218. [PubMed: 11797309]
10. Regan D, Neima D. Low-contrast letter charts in early diabetic retinopathy, ocular hypertension, glaucoma, and Parkinson's disease. Br J Ophthalmol. 1984; 68(12):885–889. [PubMed: 6509009]
11. Mwanza JC, Oakley JD, Budenz DL, Chang RT, Knight OJ, Feuer WJ. Macular ganglion cell-inner plexiform layer: automated detection and thickness reproducibility with spectral domain-optical coherence tomography in glaucoma. Invest Ophthalmol Vis Sci. 2011; 52(11):8323–8329. [PubMed: 21917932]
12. Airaksinen PJ, Alanko HI. Effect of retinal nerve fibre loss on the optic nerve head configuration in early glaucoma. Graefes Arch Clin Exp Ophthalmol. 1983; 220(4):193–196. [PubMed: 6884783]
13. Inuzuka H, Kawase K, Yamada H, Oie S, Kokuzawa S, Yamamoto T. Macular ganglion cell complex thickness in glaucoma with superior or inferior visual hemifield defects. J Glaucoma. 2014; 23(3):145–149. [PubMed: 24042125]
14. Nouri-Mahdavi K, Nowroozizadeh S, Nassiri N, et al. Macular ganglion cell/inner plexiform layer measurements by spectral domain optical coherence tomography for detection of early glaucoma and comparison to retinal nerve fiber layer measurements. Am J Ophthalmol. 2013; 156(6):1297–1307. e1292. [PubMed: 24075422]
15. Tan O, Li G, Lu AT, Varma R, Huang D. Mapping of macular substructures with optical coherence tomography for glaucoma diagnosis. Ophthalmology. 2008; 115(6):949–956. [PubMed: 17981334]
16. Wang M, Hood DC, Cho JS, et al. Measurement of local retinal ganglion cell layer thickness in patients with glaucoma using frequency-domain optical coherence tomography. Arch Ophthalmol. 2009; 127(7):875–881. [PubMed: 19597108]
17. Quellec G, Lee K, Dolejsi M, Garvin MK, Abramoff MD, Sonka M. Three-dimensional analysis of retinal layer texture: identification of fluid-filled regions in SD-OCT of the macula. IEEE Trans Med Imaging. 2010; 29(6):1321–1330. [PubMed: 20363675]
18. Mishra A, Wong A, Bizheva K, Clausi DA. Intra-retinal layer segmentation in optical coherence tomography images. Opt Express. 2009; 17(26):23719–23728. [PubMed: 20052083]

19. Garvin MK, Abramoff MD, Wu X, Russell SR, Burns TL, Sonka M. Automated 3-D intraretinal layer segmentation of macular spectral-domain optical coherence tomography images. IEEE Trans Med Imaging. 2009; 28(9):1436–1447. [PubMed: 19278927]
20. Fabritius T, Makita S, Miura M, Myllyla R, Yasuno Y. Automated segmentation of the macula by optical coherence tomography. Opt Express. 2009; 17(18):15659–15669. [PubMed: 19724565]
21. DeBuc DC, Somfai GM, Ranganathan S, Tatrai E, Ferencz M, Puliafito CA. Reliability and reproducibility of macular segmentation using a custom-built optical coherence tomography retinal image analysis software. J Biomed Opt. 2009; 14(6):064023. [PubMed: 20059261]
22. Ishikawa H, Stein DM, Wollstein G, Beaton S, Fujimoto JG, Schuman JS. Macular segmentation with optical coherence tomography. Invest Ophthalmol Vis Sci. 2005; 46(6):2012–2017. [PubMed: 15914617]
23. Kajic V, Povazay B, Hermann B, et al. Robust segmentation of intraretinal layers in the normal human fovea using a novel statistical model based on texture and shape analysis. Opt Express. 2010; 18(14):14730–14744. [PubMed: 20639959]
24. Johnson CA, Sample PA, Cioffi GA, Liebmann JR, Weinreb RN. Structure and function evaluation (SAFE): I. criteria for glaucomatous visual field loss using standard automated perimetry (SAP) and short wavelength automated perimetry (SWAP). Am J Ophthalmol. 2002; 134(2):177–185. [PubMed: 12140023]
25. de Moraes CG, Liebmann JM, Medeiros FA, Weinreb RN. Management of advanced glaucoma: Characterization and monitoring. Surv Ophthalmol. 2016; 61(5):597–615. [PubMed: 27018149]
26. Arden GB, Jacobson JJ. A simple grating test for contrast sensitivity: preliminary results indicate value in screening for glaucoma. Invest Ophthalmol Vis Sci. 1978; 17(1):23–32. [PubMed: 621124]
27. Motolko MA, Phelps CD. Contrast sensitivity in asymmetric glaucoma. Int Ophthalmol. 1984; 7(1):45–59. [PubMed: 6706474]
28. Zulauf M, Flammer J. Correlation of spatial contrast sensitivity and visual fields in glaucoma. Graefes Arch Clin Exp Ophthalmol. 1993; 231(3):146–150. [PubMed: 8462886]
29. Korth M, Horn F, Storck B, Jonas JB. Spatial and spatiotemporal contrast sensitivity of normal and glaucoma eyes. Graefes Arch Clin Exp Ophthalmol. 1989; 227(5):428–435. [PubMed: 2806928]
30. Sample PA, Juang PS, Weinreb RN. Isolating the effects of primary open-angle glaucoma on the contrast sensitivity function. Am J Ophthalmol. 1991; 112(3):308–316. [PubMed: 1882941]
31. Tochel CM, Morton JS, Jay JL, Morrison JD. Relationship between visual field loss and contrast threshold elevation in glaucoma. BMC Ophthalmol. 2005; 5:22. [PubMed: 16159386]
32. Agrawal S, Singh V, Bhasker SK, Sharma B. Correlation of visual functions with macular thickness in primary open angle glaucoma. Oman journal of ophthalmology. 2013; 6(2):96–98. [PubMed: 24082667]
33. Harwerth RS, Carter-Dawson L, Shen F, Smith EL 3rd, Crawford ML. Ganglion cell losses underlying visual field defects from experimental glaucoma. Invest Ophthalmol Vis Sci. 1999; 40(10):2242–2250. [PubMed: 10476789]
34. Garway-Heath DF, Caprioli J, Fitzke FW, Hitchings RA. Scaling the hill of vision: the physiological relationship between light sensitivity and ganglion cell numbers. Invest Ophthalmol Vis Sci. 2000; 41(7):1774–1782. [PubMed: 10845598]
35. Kerrigan-Baumrind LA, Quigley HA, Pease ME, Kerrigan DF, Mitchell RS. Number of ganglion cells in glaucoma eyes compared with threshold visual field tests in the same persons. Invest Ophthalmol Vis Sci. 2000; 41(3):741–748. [PubMed: 10711689]
36. Quigley HA, Dunkelberger GR, Green WR. Retinal ganglion cell atrophy correlated with automated perimetry in human eyes with glaucoma. Am J Ophthalmol. 1989; 107(5):453–464. [PubMed: 2712129]
37. Tan O, Chopra V, Lu AT, et al. Detection of macular ganglion cell loss in glaucoma by Fourier-domain optical coherence tomography. Ophthalmology. 2009; 116(12):2305–2314. e2301–2302. [PubMed: 19744726]
38. Kim NR, Lee ES, Seong GJ, et al. Comparing the ganglion cell complex and retinal nerve fibre layer measurements by Fourier domain OCT to detect glaucoma in high myopia. Br J Ophthalmol. 2011; 95(8):1115–1121. [PubMed: 20805125]

39. Garas A, Vargha P, Hollo G. Diagnostic accuracy of nerve fibre layer, macular thickness and optic disc measurements made with the RTVue-100 optical coherence tomograph to detect glaucoma. Eye (Lond). 2011; 25(1):57–65. [PubMed: 20930859]
40. Panda S, Jonas JB. Decreased photoreceptor count in human eyes with secondary angle-closure glaucoma. Invest Ophthalmol Vis Sci. 1992; 33(8):2532–2536. [PubMed: 1634350]
41. Kendell KR, Quigley HA, Kerrigan LA, Pease ME, Quigley EN. Primary open-angle glaucoma is not associated with photoreceptor loss. Invest Ophthalmol Vis Sci. 1995; 36(1):200–205. [PubMed: 7822147]
42. Nork TM, Ver Hoeve JN, Poulsen GL, et al. Swelling and loss of photoreceptors in chronic human and experimental glaucomas. Arch Ophthalmol. 2000; 118(2):235–245. [PubMed: 10676789]
43. Medeiros FA, Lisboa R, Weinreb RN, Liebmann JM, Girkin C, Zangwill LM. Retinal ganglion cell count estimates associated with early development of visual field defects in glaucoma. Ophthalmology. 2013; 120(4):736–744. [PubMed: 23246120]
44. Sehi M, Zhang X, Greenfield DS, et al. Retinal nerve fiber layer atrophy is associated with visual field loss over time in glaucoma suspect and glaucomatous eyes. Am J Ophthalmol. 2013; 155(1): 73–82. e71. [PubMed: 23036570]
45. Hood DC, Raza AS, de Moraes CG, Liebmann JM, Ritch R. Glaucomatous damage of the macula. Prog Retin Eye Res. 2013; 32:1–21. [PubMed: 22995953]
46. Kim JH, Lee HS, Kim NR, Seong GJ, Kim CY. Relationship between visual acuity and retinal structures measured by spectral domain optical coherence tomography in patients with open-angle glaucoma. Invest Ophthalmol Vis Sci. 2014; 55(8):4801–4811. [PubMed: 25034596]
47. Gandolfi SA, Cimino L, Sangermani C, Ungaro N, Mora P, Tardini MG. Improvement of spatial contrast sensitivity threshold after surgical reduction of intraocular pressure in unilateral high-tension glaucoma. Invest Ophthalmol Vis Sci. 2005; 46(1):197–201. [PubMed: 15623774]
48. Pomerance GN, Evans DW. Test-retest reliability of the CSV-1000 contrast test and its relationship to glaucoma therapy. Invest Ophthalmol Vis Sci. 1994; 35(9):3357–3361. [PubMed: 8056510]
49. Evans DW, Bartlett JD, Houde B, Than TP, Shaikh A. Latanoprost-induced stabilization of central visual function in patients with primary open-angle glaucoma. J Ocul Pharmacol Ther. 2008; 24(2):224–229. [PubMed: 18355134]

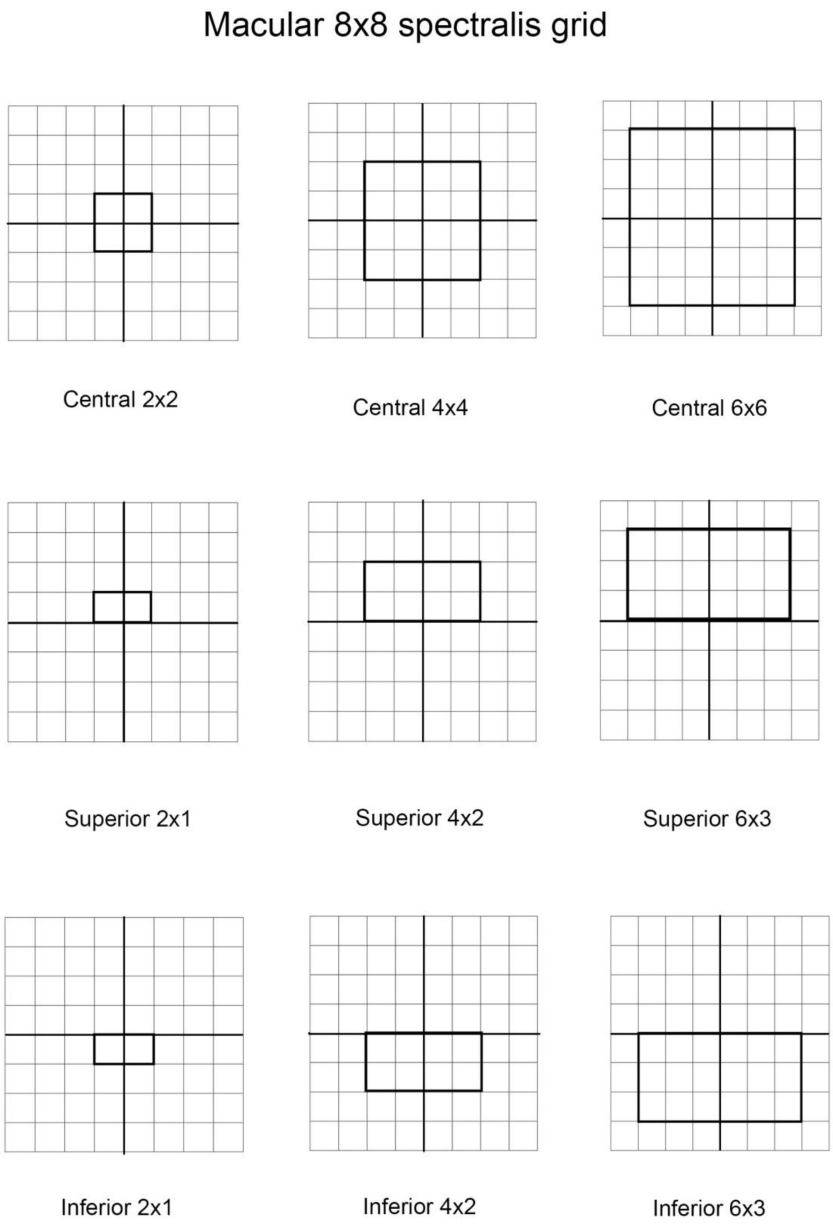

Figure 1.

Definition of macular sectors on the 8×8 array of superpixels derived from the Posterior Pole algorithm of Spectralis SD-OCT. The measurement grid is centered on the foveal center and covers the central 24×24 degrees of the posterior pole. Each superpixel is 3 degrees wide.

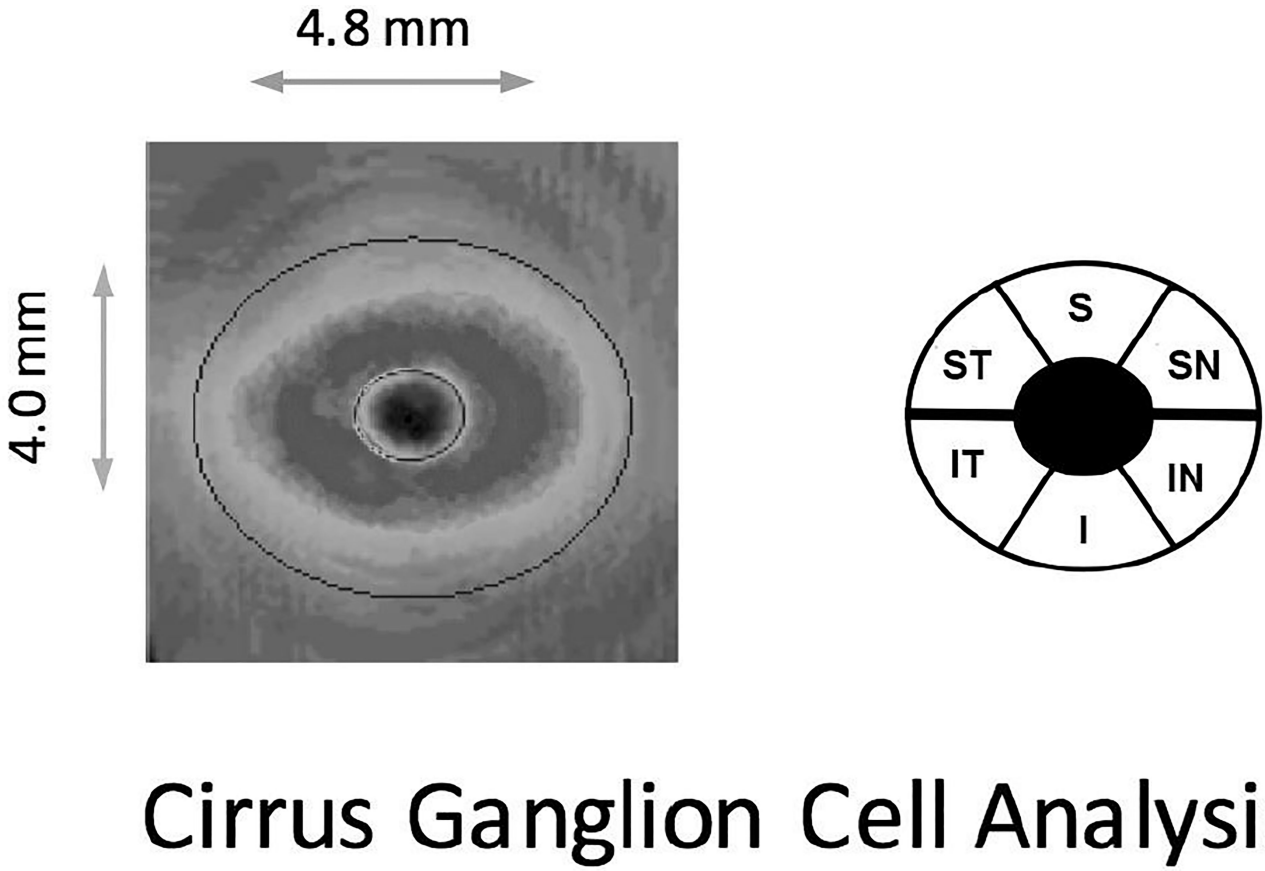

Figure 2.

The Cirrus high-definition optical coherence tomography provides ganglion cell /inner plexiform layer (GC/IPL) thickness measures in a 4.8 × 4.0 mm oval area with longer horizontal axis. The oval area is divided into 6 wedge-shaped regions and thickness measurements are provided for the superotemporal, superior, superonasal, inferonasal, inferior and inferotemporal sectors. A central oval area (1.2×1.0 mm) is excluded as the GC/IPL thickness is close to zero in this region.

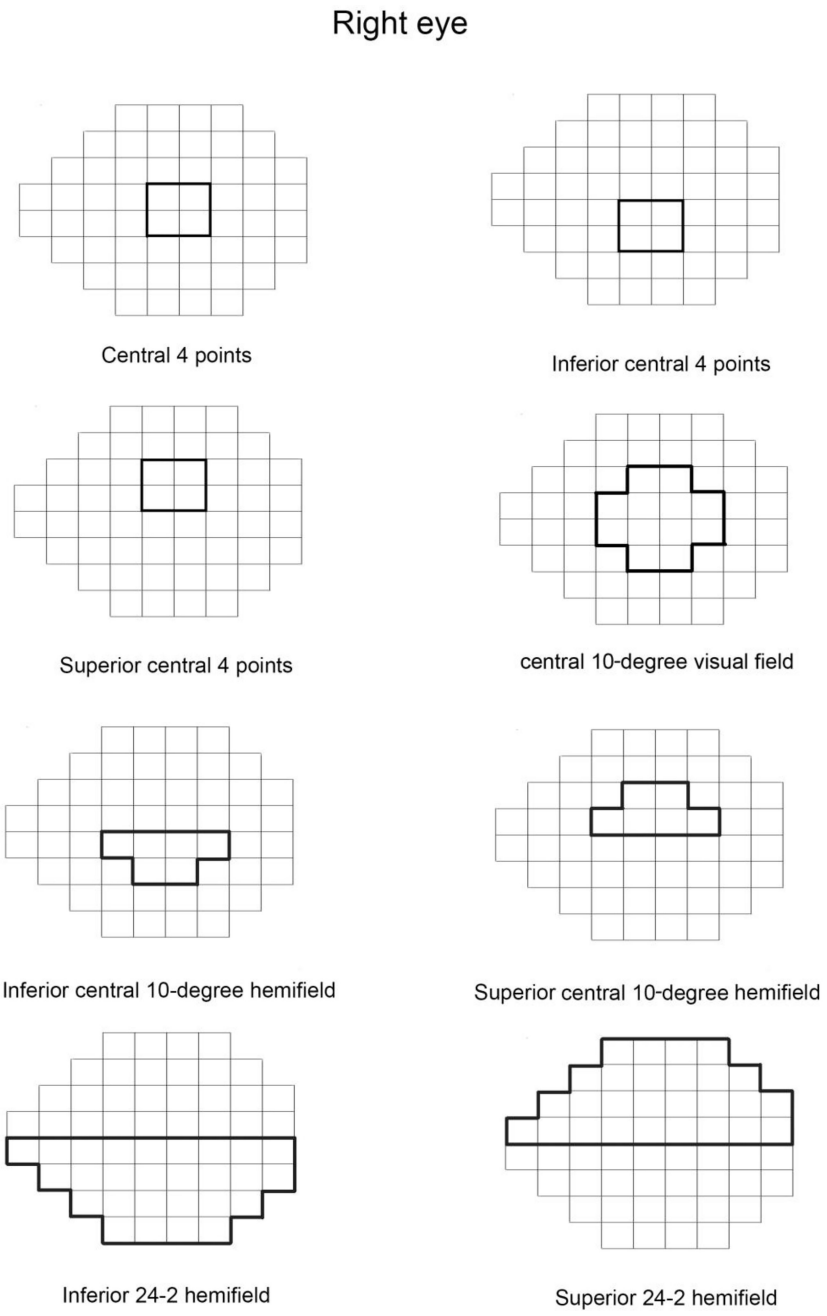

Figure 3.
The 24-2 visual field sectors defined to estimate correlations with contrast sensitivity.

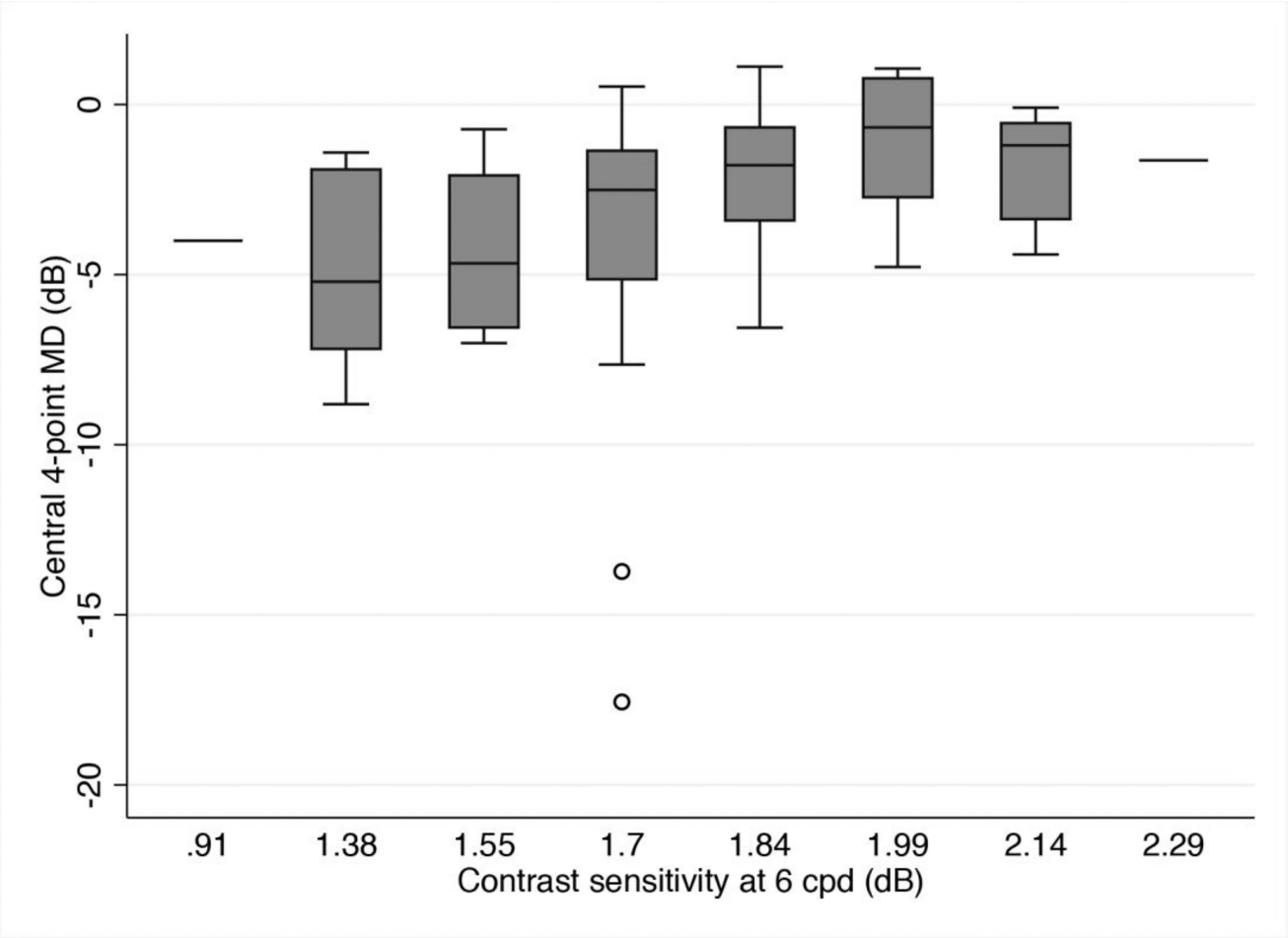

Figure 4.

Box plot demonstrating the relationship between the central 4-point mean deviation and contrast sensitivity at 6 cycles per degrees ($\rho = 0.420$; $p < 0.001$).

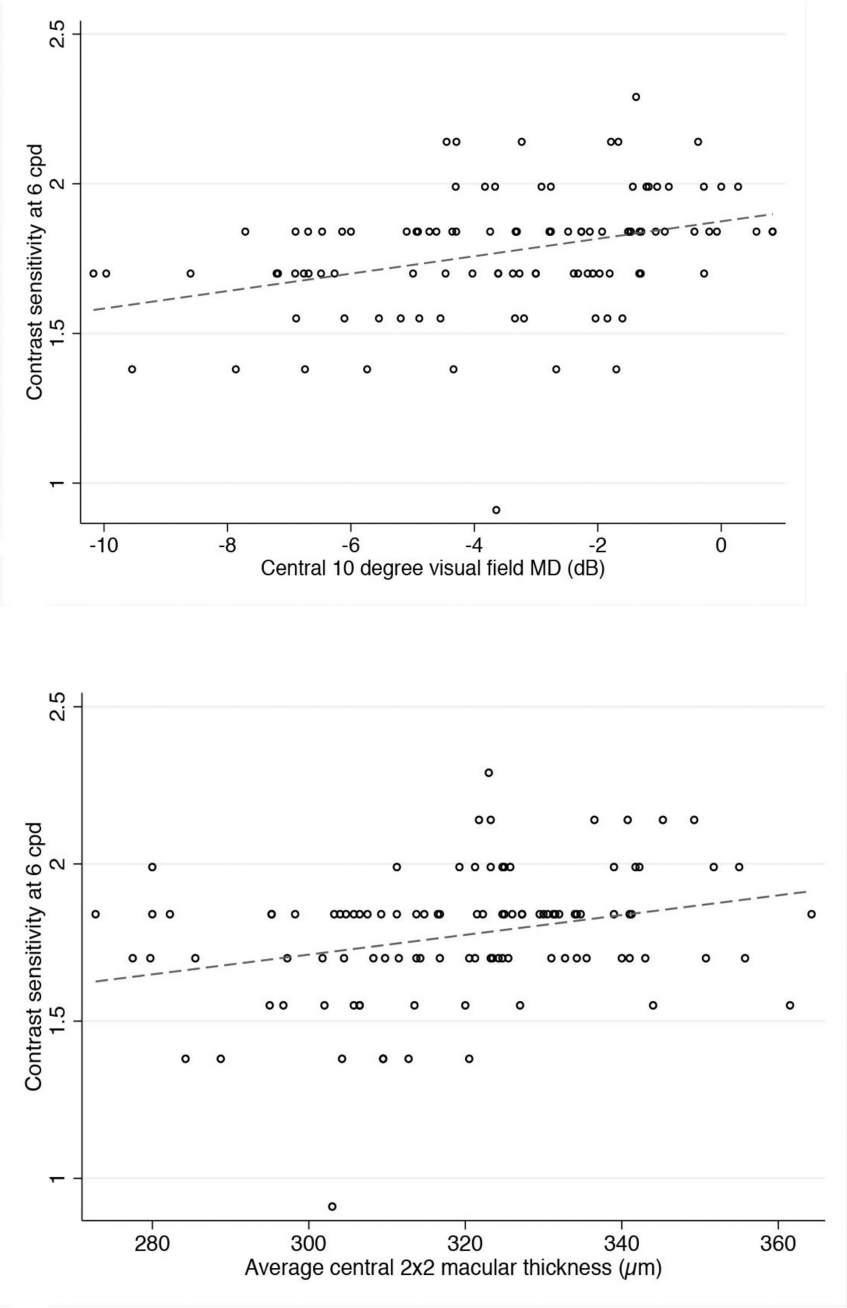

Figure 5.

Right, the scatter plot demonstrates the correlation between contrast sensitivity at 6 cycles per degree and the central 10-degree visual field mean deviation ($\rho = 0.399$, $p < 0.001$). **Left**, the scatter plot describes the correlation of contrast sensitivity at 6 cycles per degree and the average central 2×2 macular thickness ($\rho = -0.311$, $p = 0.001$) (also see Figure 1).

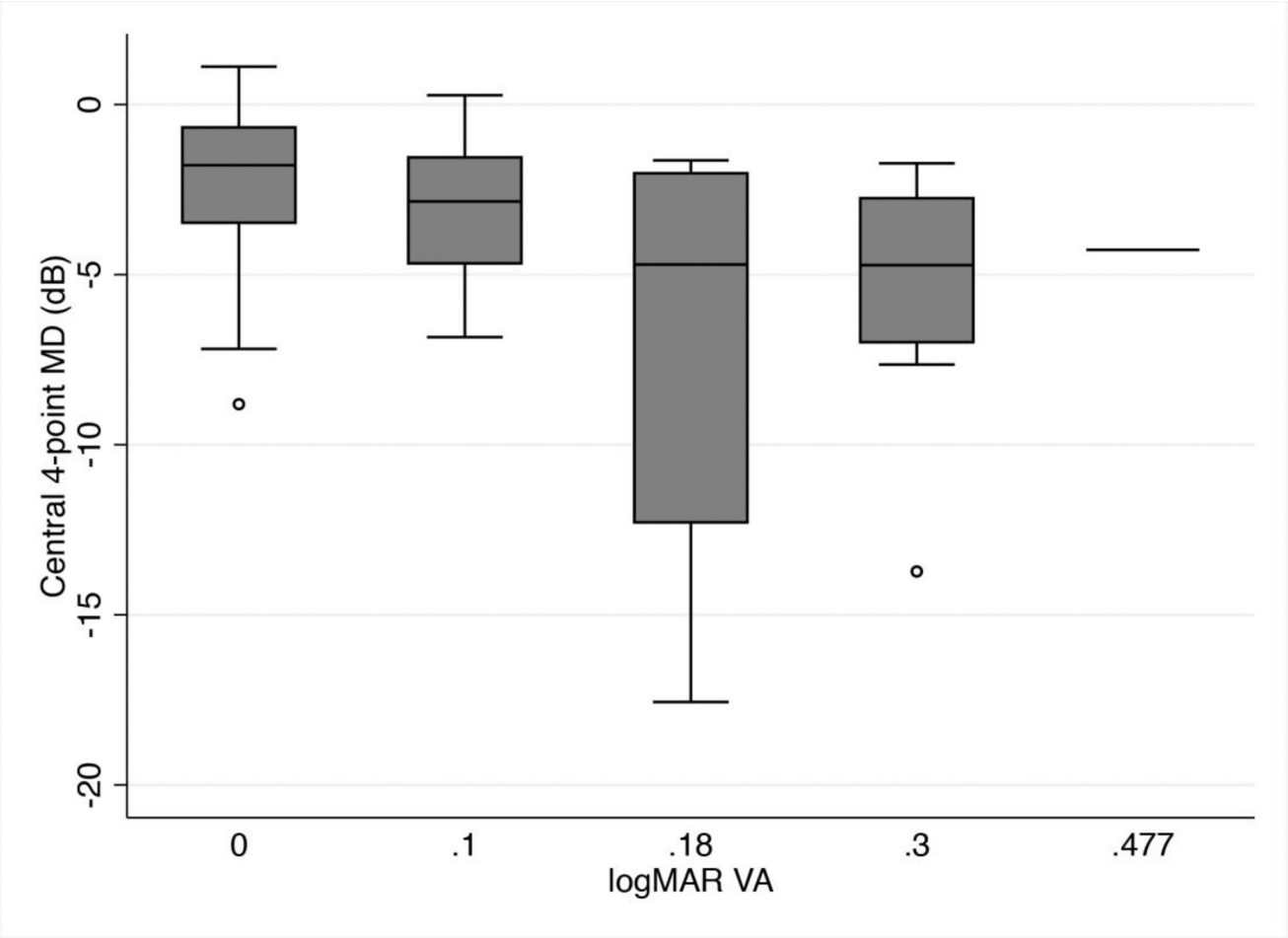

Figure 6.

Box plots display a dose-response relationship between the central 4-point mean deviation and logMAR visual acuity ($\rho = -0.329$, $p = 0.001$).

Table 1

Demographic and clinical characteristics of the study sample.

Number of eyes (patients)	105 (65)
Gender (Female/male)	36 (55.4%) / 29 (44.6%)
Age (mean ± SD[a])	67.6 (±10.4)
Lens status (phakic/pseudophakic)	61 (58.1%) / 44 (41.9%)
LogMAR visual acuity (median and IQR[b])	0 (0–0.1)
Contrast Sensitivity at 3 cpd[c] (mean ±SD)	4.65 (±1.52)
Contrast Sensitivity at 6 cpd (mean ±SD)	4.54 (±1.33)
Contrast Sensitivity at 12 cpd (mean ±SD)	4.14 (±1.73)
Contrast Sensitivity at 18 cpd (mean ±SD)	4.17 (±1.62)
24-2 visual field mean deviation (dB, median, IQR)	−7.46 (−11.08—2.97)
Average GC/IPL[d] thickness (μm, median, IQR)	64 (58–70)
Axial length (mm, mean ± SD)	24.4 (± 1.43)
IOP[e] (mmHg, mean ± SD)	**12.5 (±3.38)**

[a] SD = standard deviation

[b] IQR = interquartile range

[c] cpd = cycle per degree

[d] ganglion cell layer and inner plexiform layer

[e] Intra ocular pressure

Table 2

Median and interquartile ranges for global and sectoral visual field measurements in the study sample (leftmost column) and correlation of various visual field indices with contrast sensitivity at four different spatial frequencies. For correlation coefficients, the top number represents the ρ and the bottom number in parentheses is the p-value.

	MD[a] (median and IQR[b]), dB	CS[c] at 3 cpd[d]	CS at 6 cpd	CS at 12 cpd	CS at 18 cpd
Global MD	−7.6 (−11.1 – −3.0)	**0.227 (0.020)**	**0.287 (0.003)**	**0.285 (0.003)**	**0.236 (0.016**
Superior 24-2 hemifield	−2.80 (−6.63 – −1.18)	**0.196 (0.045)**	**0.266 (0.006)**	**0.299 (0.002)**	**0.197 (0.044)**
Inferior 24-2 hemifield	−3.43 (−5.97 – −1.55)	**0.205 (0.035)**	**0.273 (0.005)**	**0.238 (0.014)**	**0.197 (0.044)**
Central 10-degree visual field	−3.23 (−4.94 – −1.60)	**0.194 (0.047)**	**0.399 (<0.001)**	**0.371 (<0.001)**	**0.258 (0.008)**
Superior central 10-degree hemifield	−3.60 (−7.11 – −1.40)	0.149 (0.128)	**0.291 (0.003)**	**0.316 (0.001)**	0.147 (0.134)
Inferior central 10-degree hemifield	−3.07 (−4.76 – −1.59)	0.190 (0.053)	**0.350 (<0.001)**	**0.260 (0.007)**	**0.240 (0.014)**
Central 4 points	−2.12 (−4.35 – −0.73)	**0.211 (0.031)**	**0.420 (<0.001)**	**0.383 (<0.001)**	**0.228 (0.019)**
Superior central 4 points	−2.89 (−6.56 – −0.89)	0.181 (0.065)	**0.367 (<0.001)**	**0.369 (<0.001)**	0.190 (0.052)
Inferior central 4 points	−1.89 (−3.56 – −0.89)	0.163 (0.096)	**0.315 (0.001)**	**0.208 (0.033)**	0.164 (0.095)

[a] MD = mean deviation

[b] IQR = interquartile range

[c] CS = contrast sensitivity

[d] cpd = cycles per degree

Table 3

Correlation of actual visual field sensitivity indices in apostilbs with contrast sensitivity at four different spatial frequencies. For correlation coefficients, the top number represents the ρ and the bottom number in parentheses is the p-value.

Absolute mean sensitivity	CS[a] at 3 cpd[b]	CS at 6 cpd	CS at 12 cpd	CS at 18 cpd
24-2 mean sensitivity	−0.125 (0.205)	−0.160 (0.103)	−0.141 (0.151)	−0.147 (0.134)
Superior 24-2 hemifield	−0.099 (0.317)	**−0.200 (0.041)**	**−0.218 (0.026)**	−0.141 (0.154)
Inferior 24-2 hemifield	−0.114 (0.249)	−0.135 (0.170)	−0.118 (0.0231)	−0.102 (0.299)
Central 10-degree visual field	−0.125 (0.205)	**−0.200 (0.041)**	−0.141 (0.151)	−0.186 (0.058)
Superior central 10-degree hemifield	−0.113 (0.249)	**−0.237 (0.015)**	**−0.242 (0.013)**	−0.124 (0.208)
Inferior central 10-degree hemifield	−0.169 (0.085)	**−0.264 (0.006)**	**−0.213 (0.029)**	**−0.255 (0.009)**
Central 4 points	**−0.208 (0.034)**	**−0.349 (<0.001)**	**−0.275 (0.005)**	−0.155 (0.116)
Superior central 4 points	−0.116 (0.238)	**−0.250 (0.010)**	**−0.257 (0.008)**	−0.119 (0.226)
Inferior central 4 points	−0.118 (0.062)	**−0.254 (0.009)**	**−0.203 (0.038)**	−0.229 (0.0119)

[a] CS = contrast sensitivity

[b] cpd = cycle per degree

Table 4

Correlation of various visual field indices with logMAR visual acuity. For correlation coefficients, the first value represents the ρ and the second value in parentheses is the p-value.

Visual field index	logMAR VA
24-2 Visual field	**−0.307 (0.001)**
Superior 24-2 hemifield	**−0.251 (0.010)**
Inferior 24-2 hemifield	**−0.268 (0.006)**
Central 10-degree visual field	**−0.351 (<0.001)**
Superior central 10-degree hemifield	**−0.295 (0.002)**
Inferior central 10-degree hemifield	**−0.250 (0.010)**
Central 4 points	**−0.329 (0.001)**
Superior central 4 points	**−0.265 (0.006)**
Inferior central 4 points	**−0.284 (0.003)**

Table 5

Ganglion cell/inner plexiform layer (GC/IPL) sector thickness measurements and their correlation with contrast sensitivity at various measured frequencies. For correlations between contrast sensitivity and GC/IPL thickness the top number represents the ρ and the bottom number in parentheses is the p value.

	Thickness (μm) (median and IQR[a])	CS[b] at 3 cpd[c]	CS at 6 cpd	CS at 12 cpd	CS 18 cpd
Average GC/IPL	64 (58–70)	0.149 (0.129)	0.187 (0.056)	0.213 (0.829)	−0.012 (0.901)
Inferotemporal sector	60 (54–68)	0.145 (0.140)	**0.222 (0.023)**	**0.248 (0.011)**	0.059 (0.552)
Superotemporal sector	64 (55–71)	0.117 (0.233)	0.1756 (0.073)	−0.008 (0.937)	0.042 (0.674)
Superior sector	65 (57–72)	0.004 (0.969)	0.068 (0.490)	−0.043 (0.665)	−0.016 (0.872)
Superonasal sector	68 (59–77)	0045 (0.650)	0.123 (0.212)	−0.016 (0.875)	−0.030 (0.766)
Inferonasal sector	66 (58–72)	0.109 (0.268)	**0.209 (0.032)**	0.068 (0.490)	0.046 (0.643)
Inferior sector	60 (54–68)	0.0115 (0.242)	0.162 (0.099)	0.1080 (0.273)	0.047 (0.636)

[a] IQR = interquartile range

[b] CS = Contrast sensitivity

[c] cpd = cycle per degree

Table 6

Full thickness measurements in different macular sectors and their correlation with contrast sensitivity. For correlations between contrast sensitivity and full macular thickness the top number represents ρ and the bottom number in parentheses is the p value.

	Average (μm) (mean ± SD[a])	CS[b] at 3 cpd[c]	CS at 6 cpd	CS at 12 cpd	CS 18 cpd
Inferior central macular thickness (6×3 superpixels)	283.1 (±18.9	**0.208 (0.033)**	**0.228 (0.019)**	**0.214 (0.028)**	0.079 (0.424)
Central macular thickness (4×4 superpixels)	304.4 (±18.0)	**0.211 (0.031)**	**0.228 (0.020)**	0.144 (0.143)	0.117 (0.235)
Superior central macular thickness (4×2 superpixels)	306.7 (±19.6)	0.180 (0.067)	0.159 (0.105)	0.065 (0.509)	0.116 (0.239)
Inferior central macular thickness (4×2 superpixels)	302.1 (±18.9)	**0.194 (0.048)**	**0.242 (0.013)**	0.187 (0.056)	0.085 (0.387)
Central macular thickness (2×2 superpixels)	319.5 (±19.3)	**0.243 (0.012)**	**0.311 (0.001)**	**0.198 (0.043)**	0.172 (0.079)
Superior central macular thickness (2×1 superpixels)	319.7 (±20.2)	**0.216 (0.027)**	**0.273 (0.005)**	0.178 (0.070)	0.1665 (0.090)
Inferior central macular thickness (2×1 superpixels)	319.2 (±19.9)	**0.236 (0.016)**	**0.303 (0.002)**	0.182 (0.063)	0.150 (0.127)
Central macular thickness (6×6 superpixels)	286.9 (±16.8)	**0.232 (0.017)**	**0.244 (0.012)**	0.170 (0.084)	0.117 (0.233)
Superior central macular thickness (6×3 superpixels)	290.8 (±18.8)	0.172 (0.080)	0.140 (0.154)	0.028 (0.776)	0.077 (0.435)

[a] SD = standard deviation

[b] CS = contrast sensitivity

[c] cpd = cycle per degree