Structure–Function Correlations in Glaucoma Using Matrix and Standard Automated Perimetry Versus Time-Domain and Spectral-Domain OCT Devices

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Purpose. We examined the structure–function relationship between two perimetric tests, the frequency doubling technology (FDT) matrix and standard automated perimetry (SAP), and two optical coherence tomography (OCT) devices (time-domain and spectral-domain).

Methods. This cross-sectional study included 97 eyes from 29 healthy individuals, and 68 individuals with early, moderate, or advanced primary open-angle glaucoma. The correlations between overall and sectorial parameters of retinal nerve fiber layer thickness (RNFL) measured with Stratus and Spectralis OCT, and the visual field sensitivity obtained with FDT matrix and SAP were assessed. The relationship also was evaluated using a previously described linear model.

Results. The correlation coefficients for the threshold sensitivity measured with SAP and Stratus OCT ranged from 0.44 to 0.79, and those for Spectralis OCT ranged from 0.30 to 0.75. Regarding FDT matrix, the correlation ranged from 0.40 to 0.79 with Stratus OCT and from 0.39 to 0.79 with Spectralis OCT. Stronger correlations were found in the overall measurements and the arcuate sectors for both visual fields and OCT devices. A linear relationship was observed between FDT matrix sensitivity and the OCT devices. The previously described linear model fit the data from SAP and the OCT devices well, particularly in the inferotemporal sector.

Conclusions. The FDT matrix and SAP visual sensitivities were related strongly to the RNFL thickness measured with the Stratus and Spectralis OCT devices, particularly in the overall and arcuate sectors.

Keywords: glaucoma posterior segment, automated perimetry, optical coherence tomography

The functional evaluation of glaucomatous individuals is performed primarily by visual field tests. Several devices provide visual field measurements. One of the most widely used devices in clinical studies is the Humphrey Visual Field Analyzer standard automated perimeter (SAP).[1] Many studies have demonstrated that the frequency doubling technology matrix (FDT matrix perimetry) also has a good sensitivity and specificity for glaucoma detection.[2–4] This technology provides visual field measurements using stimuli consisting of alternating sinusoidal gratings at low spatial frequency and high temporal frequency.[5,6]

Structural damage is assessed through optic nerve head (ONH) and retinal nerve fiber layer (RNFL) examinations, either by clinical[7] or computerized imaging methods.[8] Among these methods, optical coherence tomography (OCT) provides relatively direct measurements of the neuroretinal rim, RNFL, and macular ganglion cell complex.[9,10] Studies have demonstrated that early versions of OCT devices, called time-domain (TD) OCT, can detect objectively patterns of reduction in average or focal parapapillary RNFL thickness.[11] The recently developed spectral-domain (SD) OCT has enhanced spatial resolution and shortened acquisition time, increasing reproducibility and performance.[12]

Structure–function models have been proposed to evaluate the relative efficacy of structural and functional tests in detecting glaucomatous damage throughout the course of the disease. Previous studies correlated the visual sensitivity and neural loss measured by histological analysis.[13,14] More recently, other studies have based their evaluations on structural changes in RNFL thickness and ONH parameters.[15–17] Indeed, structure–function models have been used to identify associations between retinal ganglion cells (RGC) estimations obtained from functional tests in healthy individuals and RNFL thickness,[18] and to predict RNFL thickness reduction from progressive RGC functional loss in glaucoma suspects.[19] Nevertheless, to date and to our knowledge, none of these structure–function models has been applied to commercially available perimetry methods other than SAP.

The purpose of this study was to determine the structure–function correlations between visual field sensitivity, as measured by the FDT matrix and SAP, and parapapillary RNFL thickness, as assessed by TD- and SD-OCT devices. A further goal was to evaluate this relationship using the simple linear model proposed by Hood et al.[16]

Methods

Healthy and primary open-angle glaucoma individuals were enrolled in this observational, cross-sectional study. The Ethics

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Committee of the Federal University of Sao Paulo approved the study protocol. The research followed the tenets of the Declaration of Helsinki. All participants provided informed consent.

All patients underwent complete ophthalmic examinations, including best-corrected visual acuity measurement, slit-lamp biomicroscopy, gonioscopy, Goldmann tonometry, dilated fundus biomicroscopy, stereophotography, 24-2 SAP (Humphrey Visual Field Analyzer, Carl Zeiss Meditec, Dublin, CA, USA), and 24-2 FDT matrix (Carl Zeiss Meditec) perimetries. Clinical exams were performed within 6 months for healthy subjects and within 3 months for glaucoma patients. Both eyes were examined in each subject. If both eyes met the eligibility criteria, one eye per subject was selected randomly to be included in the study.

All healthy individuals and glaucoma patients must have had the following measurements: refractive error between ±6.00 spherical diopters and ±3.00 cylindrical diopters, and absence of macular changes or any other significant retinal disease that could interfere with the exams. All glaucoma patients were under treatment and had an IOP of <20 mm Hg. The healthy subjects had a best-corrected visual acuity of 20/40 or better, a normal optic disc, and a normal 24-2 SAP.

In addition, glaucoma patients must have had previous experience with SAP in at least two exams, a best-corrected visual acuity of 20/200 or better, signs of glaucomatous optic neuropathy, and an abnormal 24-2 SAP. Glaucomatous optic neuropathy was defined as the presence of either cup/disc asymmetry of >0.2 between the two eyes that was unexplained by asymmetry in disc size, rim thinning, peripapillary hemorrhage, or an RNFL defect.

An abnormal visual field was defined as the presence of at least one of the following criteria: Glaucoma Hemifield Test outside the normal limits, pattern standard deviation with a probability level of <5%, or a visual field defect on the pattern deviation chart. For SAP, a group of at least three adjacent points with a probability level of <5%, with 1 point having a probability level of <1%, was considered a visual field defect. The FDT matrix perimetry defect was defined by the presence of at least one point with a probability level of <1%. The visual field change was confirmed by at least one test.

The following exclusion criteria were applied: the presence of mean opacities that precluded the performance of study exams or unreliable perimetry, as defined by excessive false-positive (>10%), false-negative, or fixation loss (>20%) rates; glaucoma suspects; and patients with ocular hypertension.[20]

RNFL Measurements

The TD-OCT imaging was obtained with a Stratus OCT (Carl-Zeiss Meditec) using version 5.0.1 software. The RNFL measurements were obtained from three consecutive circular scans (each one comprised 256 A-scans) manually centered on the optic disc. Only the scans with a signal strength of ≥7 (of 10) were included.

The SD-OCT imaging was performed with a Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) with software version 5.1.3 using an eye tracking–assisted circle that was centered manually on the optic disc; the analyzed image was composed of 15 high-resolution (1536 A-scans) images. The included scans had a signal strength of >20 of 30 decibels (dB).

The Stratus OCT RNFL thickness parameters used in this study were average thickness (360° measure), superonasal (91°–135°), nasal (136°–225°), inferonasal (226°–270°), inferotemporal (271°–315°), temporal (316°–45°), and superotemporal (46°–90°). Each sector was calculated by combining clock hours thicknesses, which were available from the Stratus OCT printout. For Spectralis OCT, the sectors were selected directly

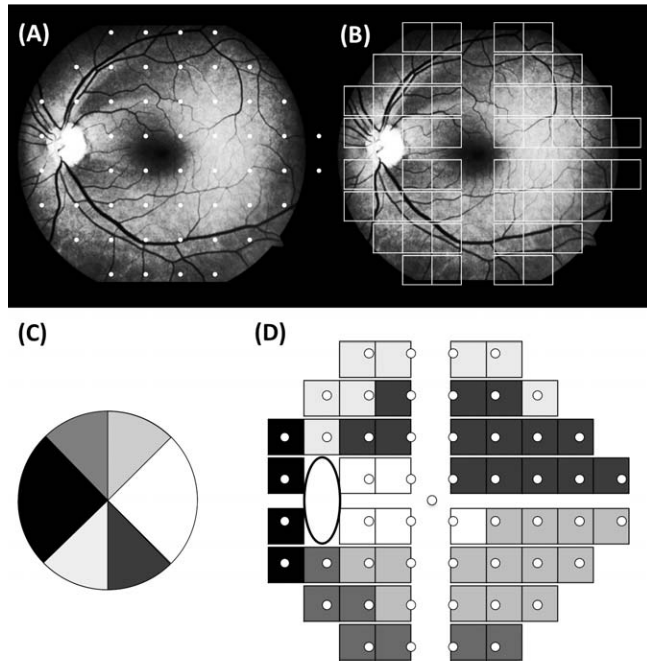

Figure 1. The schematic location of the sensitivity point distribution in 24-2 SAP (**A**) and FDT matrix perimetry (**B**) superimposed on a left eye red-free fundus image. A representative map of OCT RNFL divided in six quadrants (**C**) and the corresponding visual field sensitivity point distribution (**D**). *Small circles* represent SAP, and *squares* represent the FDT matrix perimetry stimulus locations.

from the device printout. The six sectors were selected based on the correspondence map described by Garway-Heath et al.[21] (Fig. 1).

Visual Sensitivity Testing

Visual sensitivity was determined using SAP and FDT matrix perimetry. The SAP was performed using the 24-2 program with a Swedish interactive threshold algorithm (SITA) standard protocol and a standard Goldmann size III stimulus (diameter 0.43°). The FDT was performed with the 24-2 zippy estimation and sequential testing (ZEST) threshold algorithm.

Visual field sensitivity is expressed conventionally on a dB (logarithmic) scale. To correlate visual field data to RNFL thickness measurements, sensitivity was converted to a linear scale. In SAP, the dB measurement is 10 times the log of the reciprocal of the light stimulus intensity, as measured in lamberts (L) according to the equation $dB = 10 \log_{10}(1/L)$.[15] In FDT matrix perimetry, sensitivities are expressed as the reciprocal of the Michelson contrast (C) with 20 dB per log unit ($dB = 20 \log_{10}[1/C]$).[5] Therefore, the following formulas were applied, where T represents the exponential or antilog scale:

$$T = 10^{(\mathrm{dB}/10)}$$

for the SAP sensitivity, and

$$T = 10^{(\mathrm{dB}/20)}$$

for the FDT matrix perimetry sensitivity.

The points tested using the SAP and FDT matrix perimetry methods were averaged into six sectors according to the OCT RNFL quadrants using the map proposed by Garway-Heath et al.[21] (Fig. 1). Each sector average was transformed back into logarithmic (dB) scale.

Table 1. Structural and Functional Characteristics of Healthy Participants and the Glaucoma Group

		Glaucoma Group, $n = 68$		
	Healthy, $n = 29$	**Early, $n = 20$**	**Moderate, $n = 18$**	**Advanced, $n = 30$**
Age, mean (SD)	54.7 (7.87)	61.5 (11.17)	65.39 (13.83)	63.5 (12.75)
Sex, female (%)	19 (65.5)	13 (65)	9 (50)	15 (50)
Race, white (%)	16 (55.2)	11 (55)	11 (61.2)	14 (46.67)
SAP MD, mean (SD), dB	−0.52 (1.11)	−1.11 (0.94)	−4.18 (0.92)	−12.9 (6.92)
FDT matrix MD, mean (SD), dB	0.09 (2.79)	−1.29 (3.67)	−5.74 (3.58)	−11.72 (5.85)
Stratus OCT AT, mean (SD), μm	96.18 (12.6)	82.88 (15.97)	74.50 (13.86)	58.33 (13.3)
Spectralis OCT AT, mean (SD), μm	100.89 (10.42)	88.15 (14.57)	80.5 (14.89)	64.17 (11.94)

AT, average thickness.

Statistical Analysis

Structure–function correlations between visual field sensitivity thresholds and RNFL thickness were reported as Spearman's rank correlation coefficients (r). Spearman's correlation coefficient is a statistical measure of strength of a monotonic relationship between paired data. Unlike Pearson's correlation, there is no requirement of normality or linearity, and Spearman's correlation, therefore, is a nonparametric statistic.[22] Correlations of <0.4 were rated as weak; correlations of ≥0.4 and <0.6 were classified as moderate, and correlations of ≥0.6 were classified as strong.

The simple linear model proposed by Hood et al.[16] was applied to predict the change in RNFL thickness from visual field losses measured with SAP and FDT matrix perimetries for the arcuate (superotemporal and inferotemporal) regions. Hood et al.[16] assumed that the RNFL (R) has 2 components, RGC axons (S_o) and a residual component (b) composed of glial cells and retinal vessels. As the visual field sensitivity decreases, the S_o value decreases, but b remains constant. The relationship between S_o and sensitivity loss is linear when the dB scale of the visual field is converted to a linear scale (antilog). These assumptions can be represented by Equations 1 and 2:

$$R = S_o + b, \quad \text{when } T \geq 1.0\,(TD \geq 0) \quad (1)$$

and

$$R = S_o T + b, \quad \text{when } T < 1.0\,(TD < 0), \quad (2)$$

where T is the relative linear visual sensitivity loss and corresponds to the antilog of the total deviation value (TD). When the sensitivity is normal or greater than normal ($T \geq 1.0$ or $TD \geq 0$), it is independent of the RNFL thickness.

Residual component b was determined for both visual fields as the mean RNFL thickness obtained from the Stratus and Spectralis OCT devices for the patients with an SAP mean deviation (MD) worse than −10 dB and the patients categorized as Stage 4 or 5 on Brusini's FDT Staging System 2.[23] The S_o was calculated as the difference between the mean RNFL thickness of the normal individuals and residual component b. The goodness of fit between our sample and the model provided by Hood et al.[16] was evaluated with the coefficient of determination (R^2). In general, a model fits the data well if the differences between the observed values and the model's predicted values are small. The coefficient of determination R^2 is a statistical measure of how well a model explains the variability in observed data.

For Spearman's correlation coefficient and the coefficient of determination, a P value of <0.01 was considered statistically significant. The statistical analysis was performed with Stata (version 10.0; StataCorp, College Station, TX, USA).

Results

There were 97 eyes in 97 individuals enrolled in the study: 29 healthy eyes and 20, 18, and 30 eyes with early, moderate, and advanced or severe glaucoma, respectively.[24] Table 1 shows the demographic data for each group. Of the individuals, 56 were female and 52 were Caucasian. The mean patient age was 60.8 years (range, 38–85 years): 54.6 years in the healthy group and 63.4 years in the glaucoma group. The average SAP MD was −5.1 dB (range, −32.3–1.4 dB): −0.52 dB for the healthy patients and −7.13 dB for the glaucoma patients. Considering the FDT matrix perimetry group, the average MD was −4.9 dB (range, −24.8–5.0 dB), 0.09 dB for the healthy patients and −7.07 dB for the glaucoma group.

The Spearman correlations between RNFL thicknesses measured in linear scale and visual field sensitivity expressed in dB ranged from 0.30 to 0.79 for SAP and from 0.39 to 0.79 for FDT matrix (Table 2). The temporal and nasal sectors showed weaker correlations than the other sectors, ranging from 0.30 to 0.51 for SAP and from 0.40 to 0.43 for FDT matrix. Stronger correlations were found in the arcuate sectors, the inferotemporal sector (0.79 for SAP and FDT matrix perimetry) and the superotemporal sector (0.69, SAP; 0.68, FDT matrix perimetry) as well as in the overall measurements (0.73, SAP; 0.69, FDT matrix perimetry). All correlations were statistically

Table 2. Structure–Function Relationship Between Visual Field Sensitivity Measured With SAP or FDT Perimetry and RNFL Thickness Measured With Stratus or Spectralis OCT Devices

	Visual Field	
Sector	**SAP, r**	**FDT Matrix, r**
Stratus OCT		
Superotemporal	0.69*	0.68*
Inferotemporal	0.79*	0.79*
Temporal	0.44*	0.43*
Superonasal	0.62*	0.62*
Inferonasal	0.68*	0.64*
Nasal	0.51*	0.40*
Overall	0.73*	0.68*
Spectralis OCT		
Superotemporal	0.66*	0.66*
Inferotemporal	0.75*	0.79*
Temporal	0.30	0.39*
Superonasal	0.55*	0.55*
Inferonasal	0.61*	0.60*
Nasal	0.47*	0.42*
Overall	0.69*	0.69*

* $P < 0.01$. r, Spearman correlation coefficient.

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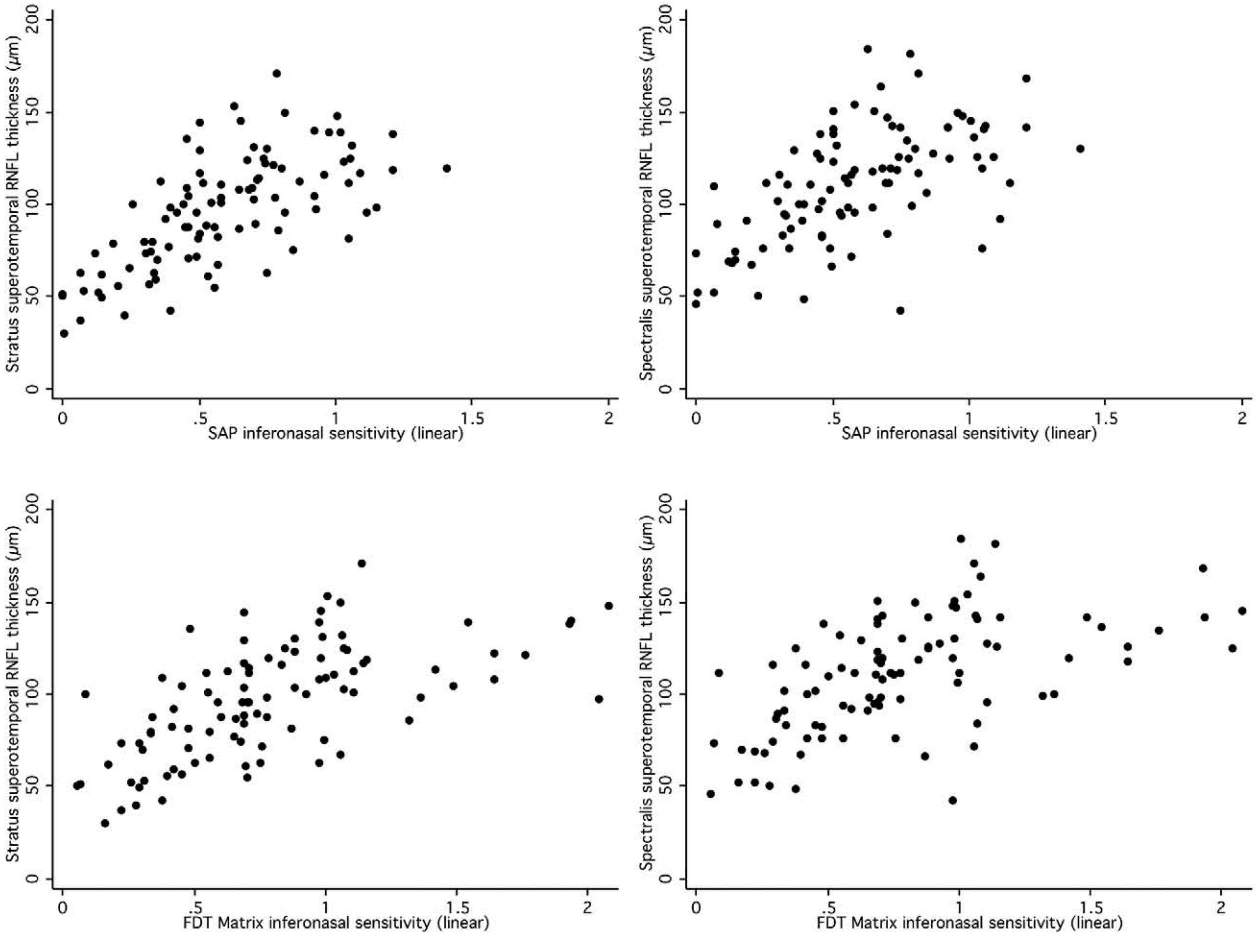

FIGURE 2. Correlations between the visual field sensitivity and RNFL measured by the OCT devices in the superotemporal sector. The *vertical axis* shows the RNFL thickness measured in micrometers (μm) for the Stratus (*left*) and Spectralis (*right*) OCT devices. The *horizontal axis* shows the visual field sensitivity measured in a linear scale for SAP (*top*) and FDT perimetry matrix (*bottom*).

significant, with the exception of the correlation between SAP and Spectralis OCT in the temporal sector ($P = 0.029$).

Considering the relationship between Stratus OCT and the visual fields, similar correlations were found with SAP and FDT matrix. There was a trend toward stronger correlations with SAP, particularly for the overall measurements, and the inferonasal and nasal sectors when compared to FDT matrix. Spectralis OCT also had a similar relationship with both visual fields that was slightly stronger with FDT matrix in the inferotemporal and temporal sectors, and with SAP in the nasal sector (Table 2).

Similar relationships also were observed between FDT matrix and both OCT devices. There was a trend toward stronger correlations with Stratus OCT, particularly in the superonasal and inferonasal sectors. Although similar, the SAP relationships tended to be stronger with Stratus OCT for all sectors tested (Table 2).

Scatterplot graphics of the visual field sensitivity expressed in linear scale and RNFL thickness for the arcuate sectors suggested linear relationships between both visual fields and OCT devices (Figs. 2, 3).

The goodness of fit between the RNFL thickness measured by Stratus or Spectralis OCT and the RNFL predicted by SAP or FDT matrix perimetry using the model of Hood et al.,[16] as determined by the coefficient of determination for the arcuate sectors, is shown in Table 3. All coefficients were statistically significant and ranged from 0.31 to 0.74. The best fit for our data and the model of Hood et al.[16] was found for RNFL estimates from SAP values and Stratus OCT, particularly in the inferotemporal sector. The worst fit was found between FDT matrix RNFL estimates and Spectralis OCT.

DISCUSSION

This study showed that the RNFL thickness measured with the Stratus and Spectralis OCT devices was consistently related to the visual field sensitivity measured with SAP and FDT matrix perimetry. Strong and similar correlations were observed in the overall measurements and arcuate sectors for the Stratus and Spectralis OCT devices, and the two visual fields. Structure–function relationships with TD- and SD-OCT were compared previously using different methodologies. Leung et al.[25] correlated the mean deviation and average RNFL measurements, and observed no significant difference in the correlation strength for Cirrus OCT and Stratus OCT. Takagishi et al.[26] also found similar structure–function relationships using Stratus and Cirrus OCT devices, with significant correlations for all but the nasal sector.

Structure–function correlations also were similar for SAP and FDT matrix perimetry. Strong correlations were observed for the FDT matrix and SAP threshold sensitivities in the overall and arcuate sectors and the OCT devices. Weak to moderate correlations were found in the nasal (0.40–0.51) and temporal (0.30–0.44) sectors, likely because there are fewer visual field

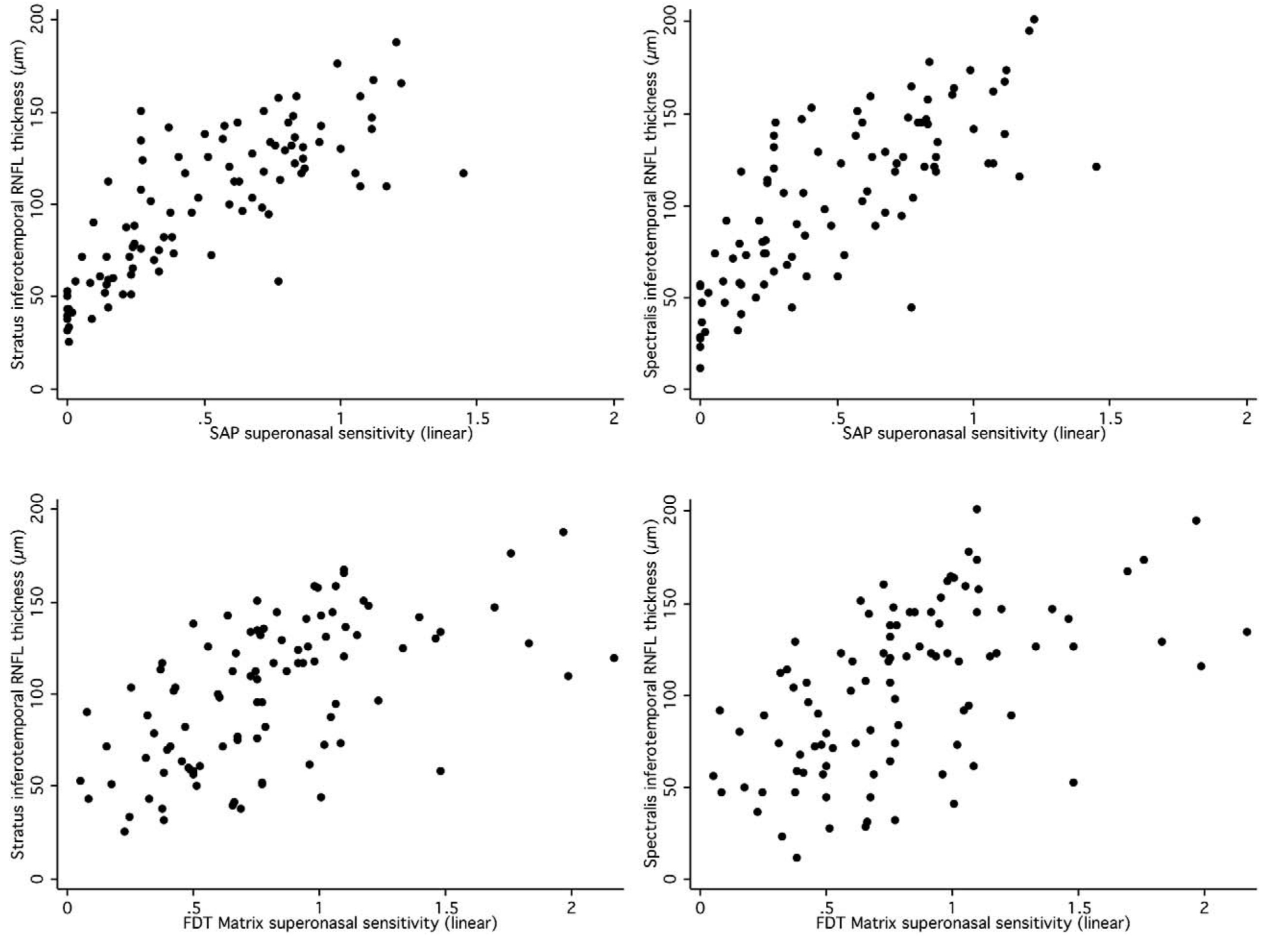

FIGURE 3. Correlations between the visual field sensitivity and RNFL measured by the OCT devices in the superotemporal sector. The *vertical axis* shows the RNFL thickness measured in micrometers (μm) for the Stratus (*left*) and Spectralis (*right*) OCT devices. The *horizontal axis* shows the visual field sensitivity measured in a linear scale for SAP (*top*) and FDT perimetry matrix (*bottom*).

test points in these sectors, resulting in poorer precision.[15] Other studies have evaluated such correlations; Hirashima et al.[27] found no significant associations between the FDT matrix indices and RNFL measured with RTvue-100. Additionally, Lamparter et al.[28] reported weak to moderate structure–function correlations between HRT and flicker-defined perimetry, FDT matrix perimetry, and SAP. These investigators[28] recorded sensitivity using the same antilog scale for all visual fields.

Structure–function models provide a framework of the relationship between structural and functional tests throughout the course of glaucoma. Each model incorporates elements that could influence the structure and function relationship, such as measurement scale,[21] eccentricity from the fovea,[17] and RNFL residual components (glia and vessels).[16] The simple linear model of Hood et al.[16] was described originally to evaluate the relationship between the linear sensitivity loss on SAP and multifocal visual evoked potential, and was used later for Stratus OCT. This model also has shown good fit with other structural tests, such as Cirrus OCT[29] and RTVue OCT.[30] Using the model of Hood et al.,[16] differences have been observed between the Stratus OCT and SD-OCT devices, particularly regarding the RNFL residual thickness (*b*). The *b* values were higher for the SD-OCT devices, which was explained by the low number of advanced glaucoma patients (MD < 10 dB) included in their data.[29,30]

In our study, the model of Hood et al.[16] performed best (0.74) when using Stratus structural measurements and SAP sensitivity, and performed least (0.31) well when using the Spectralis structural measurements and FDT matrix perimetry sensitivity. A good fit was observed between the Spectralis OCT measurements and the estimates obtained using SAP sensitivity (0.66). The *b* values were similar for both OCT devices for the inferotemporal sector (Stratus, 56.37 μm; Spectralis, 54.29 μm), but higher for Spectralis (80.81 μm; Stratus, 66.47 μm) in the superotemporal sector. This could have worsened the correlation in the superotemporal sector between SAP and Spectralis OCT. Moreover, regressions using

TABLE 3. Correlations Between RNFL Thickness Measured by Stratus and Spectralis OCT Devices and Predicted by SAP and FDT Perimetry

	Visual Field	
Sector	**SAP, R^2**	**FDT Matrix, R^2**
Stratus OCT		
Superotemporal	0.55*	0.44*
Inferotemporal	0.74*	0.35*
Spectralis OCT		
Superotemporal	0.42*	0.36*
Inferotemporal	0.66*	0.31*

* $P < 0.01$. R^2, coefficient of determination.

the FDT matrix sensitivity data did not demonstrate a good fit for the data from Stratus or Spectralis OCT (0.31–0.44).

Although no model is designed to predict structural damage from FDT matrix sensitivity loss, the relationship observed between the sensitivity expressed on a linear scale and the OCT measurements revealed interesting results. In addition to the strong correlations found in the overall and arcuate sectors, the scatterplots suggested a linear association with both OCT devices. The linear associations observed could be related to the functional ability of the test to detect sensitivity loss in the early and advanced stages of the disease. Medeiros et al.[3] observed a significantly better performance of FDT matrix compared to SAP for diagnosing glaucoma in early stages. Moreover, Artes et al.[6] found a lower proportion of absolute defects (threshold estimates of 0 dB) with FDT matrix than SAP, which might have reduced the floor effect with FDT matrix perimetry.

One limitation of this study is that it was not possible to select patients with previous experience with FDT matrix perimetry because of the limited equipment availability; however, patients with visual field abnormality underwent at least one additional visual field test. Furthermore, to our knowledge there are no studies evaluating the FDT matrix perimetry test points corresponding to the RNFL sectors. Considering the structure–function models, an evaluation of the macular ganglion cell complex could improve the correlations because glaucoma can affect the macular region even in the early stages.[31]

In summary, structure–function correlations between the visual fields and OCT devices were strong in the overall and arcuate sectors. The FDT matrix sensitivity loss and RNFL damage measured with the OCT devices were consistently related throughout the different stages of the disease. Combining FDT matrix perimetry and OCT measurements may improve the diagnostic capacity and the ability to detect glaucoma progression, as already has been demonstrated for SAP.[32]

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