Glaucoma

Mapping the Central 10° Visual Field to the Optic Nerve Head Using the Structure–Function Relationship

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Submitted: November 26, 2017
Accepted: April 26, 2018

PURPOSE. To investigate the structure–function mapping in the central 10° by relating Humphrey field analyzer (HFA) 10-2 visual field (VF) and circumpapillary retinal nerve fiber layer (cpRNFL) thickness from spectral-domain optical coherence tomography (SD-OCT). We also compared the obtained results with a previously reported mapping between 10-2 VF and the optic disc.

METHODS. In 151 eyes of 151 POAG patients and 35 eyes from 35 healthy participants, cpRNFL thickness measurements were obtained using SD-OCT and the 10-2 VF was measured with the HFA. The relationship between visual sensitivity and cpRNFL thickness values in the temporal 180° was analyzed using least absolute shrinkage and selection operator (LASSO) regression. The optic disc angle corresponding to each VF test point was then derived using the coefficients from the optimal LASSO regression.

RESULTS. The structure–function map obtained was largely consistent with the mapping reported previously; superior central VF test points correspond to a more vulnerable area of the optic disc, more distant toward the inferior pole from the center of the temporal quadrant (9:00 o’clock for the right eye) while inferior VF test points correspond closer to the center of the temporal quadrant. The prediction error tended to be large in the ‘more vulnerable area’ in the map reported previously.

CONCLUSIONS. The structure–function map obtained largely confirms the previously reported map; however, some important differences were observed.

Keywords: glaucoma, optical coherence tomography, photoreceptor, visual field

Glucomatous visual field (VF) damage is usually evaluated using a central 24° or 30° VF test, such as the 24-2 VF with the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Dublin, CA, USA) which is presented as a 6° grid. The relationship between the VF and the retinal nerve fiber layer (RNFL) is often referred to as the structure–function relationship. Garway-Heath et al.1 proposed a structure–function mapping based on annotated fundus photographs. Recent developments in spectral-domain optical coherence tomography (SD-OCT) have enabled a very accurate assessment of circumpapillary retinal nerve fiber layer (cpRNFL) thickness, and the structure–function relationship has been derived between OCT images and the 24-2 VF.2–5

Studies have revealed that, in a considerable number of eyes, the 24-2 VF is not sufficient to evaluate glaucomatous damage in the central VF area, and it is recommended to use a 10-2 VF test.5–10 In Hood et al.,11,12 it was suggested that VF tests based on a 6° grid (like the 24-2 test) should be replaced because early glaucomatous damage of the macula can be missed or underestimated. The purpose of the current study was to investigate the structure–function mapping in the central by 10° by relating HFA 10-2 VF sensitivity and cpRNFL thickness measurements using the strength of the relationship between SD-OCT measured cpRNFL thickness and 10-2 HFA VF sensitivity. Due to the large number of variables investigated, least absolute shrinkage and selection operator (LASSO) regression was used to investigate the strength of the structure–function relationship. LASSO regression is similar to standard linear regression, but reduces the likelihood of over fitting the data by assigning spurious variables a coefficient value of zero (i.e., excluding them from the final model) with the L1 regularization (adds penalty equivalent to absolute value of the magnitude of coefficients); other variables, regarded as significantly related to the dependent variable, are included in the model. Ridge regression analysis is a similar approach, but uses L2 regularization (adds penalty equivalent to square of the magnitude of coefficients), and LASSO regression usually outperforms ridge regression, unless coefficients for all variables are roughly of equal size.13

We also compare the obtained results with the mapping generated by Hood et al.,11 in which it was suggested that the macular retinal region can be divided into two regions: a vulnerable area (where the inferior macular region of the retina enters the inferior quadrant of the optic disc) and a less vulnerable area (where the superior macular region and the
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MATERIALS AND METHODS

The Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine at the University of Tokyo, Inoue Eye Hospital, and JR Tokyo General Hospital approved the study. Written informed consent was given by participants for their information to be stored in the hospital database and used for research. This study was performed according to the tenets of the Declaration of Helsinki.

Subjects

The study population consisted of 151 eyes of 151 POAG patients and 35 eyes from 35 healthy participants. All study participants were enrolled between 2013 and 2016 at the University of Tokyo Hospital, the Inoue Eye Hospital, or the JR Tokyo General Hospital. All subjects underwent complete ophthalmic examinations, including biomicroscopy, gonioscopy, IOP measurement, funduscopy, refraction, best-corrected visual acuity measurements, and axial length measurements, as well as OCT imaging and VF testing.

POAG was defined as (1) presence of typical glaucomatous changes in the optic nerve head such as a rim notch with a rim width ≤ 0.1 disc diameters or a vertical cup-to-disc ratio > 0.7 and/or a RNFL defect with its edge at the optic nerve head margin greater than a major retinal vessel, diverging in an arcuate or wedge shape, and (2) gonioscopically wide open angles of grade 3 or 4 based on the Shaffer classification. Exclusion criterion were (1) age < 20-years old, (2) possible secondary ocular hypertension in either eye, (3) visual acuity ≤ 0.5 LogMAR,14 and (4) axial length shorter than 22.0 or longer than 26.0 mm. Thus, the diagnosis of POAG was made irrespective of the presence of glaucomatous VF change so that patients with a large range of glaucomatous damage were enrolled in the study, including those without measurable VF damage. Subjects with other systemic or ocular disorders that might affect VF results were carefully excluded. If both eyes of a patient satisfied these criteria, one eye was randomly chosen.

VF Data

VF testing was performed using the HFA with the 10-2 program (SITA-Standard and Goldmann III target). All participants were subjected to near refractive correction and all had previous experience in VF examinations. Unreliable VFs defined as fixation losses > 20%, or false-positive responses > 15% were excluded,15 following the manufacturer’s recommendation.

OCT Data

SD-OCT data were obtained using the RS-3000 (Nidek Co., Ltd., Aichi, Japan) within a period of 3 months from the VF measurement. Measurements were performed after pupillary dilation with mydriatic drug (1% tropicamide; Santen Pharmaceutical Co., Ltd., Osaka, Japan), and OCT imaging was performed using the protocol raster scan, and a 6.0 × 6.0-mm² area (512 × 128 pixels). Data with a signal strength index < 7 were excluded as recommended by the manufacturer. Images affected by eye movements, involuntary blinking, or saccades were also carefully excluded. The cpRNFL thickness was measured at 1024 points (approximately every 0.35°), from the most temporal side toward the clockwise direction (9 o’clock position, right eye: 0°; for example 350° is identical to −10°), and the 513 cpRNFL thickness values corresponding to the temporal 180° were used in the analysis.

Statistical Analysis

First, the correlation between each of cpRNFL thickness 1024 points and total deviation (TD) values at each test point on the 10-2 HFA VF, following the study by Gardiner et al16 Then, the relationship between each total deviation value (dB) and the 513 cpRNFL thickness values in the temporal 180° (from −90° to 90° via 360 = 0°) was also analyzed using LASSO regression, so that a optic disc angle corresponds to each VF test point was identified. In this study, cpRNFL thickness was measured every 0.35° and 513-cpRNFL thickness values, corresponding to the temporal 180°, were used in the analysis. With such a large number of variables, it is not appropriate to apply standard ordinary least squares linear regression (OLSLR); hence, LASSO regression was used. LASSO regression is similar to OLSLR, but different in that the sum of the absolute values of the regression coefficients is constrained (penalized); the optimal penalty value is decided by minimizing the prediction error in cross validation. Thus, LASSO regression reduces the likelihood of over fitting the data by assigning redundant variables a coefficient value of zero (i.e., excluding them from the final model); other variables, regarded as significantly related to the dependent variable, are included in the model. LASSO regression is especially useful when the number of independent variables is large because it is likely that some predictors are spurious associated with the outcome value. Specifically, if x ∈ R⁶ denotes the independent variables and y ∈ R denotes the response (please note xij are normalized, but the coefficients in the final model were returned on the original scale, and y has mean zero), the Lasso algorithm applies a penalty as follows:

\[
\min_{(\beta_0, \beta) \in \mathbb{R}^{n+1}} \left[ \frac{1}{2N} \sum_{i=1}^{N} (y_i - \beta_0 - \mathbf{x}_i^T \beta)^2 + \lambda P_\lambda(\beta) \right].
\]

\[
P_\lambda(\beta) = (1 - \lambda \alpha) \frac{1}{2} \sum_{j=1}^{p} |\beta_j|^2 + \lambda |\beta_j|_1 \tag{2}
\]

In Equation 1, \( \lambda P_\lambda(\beta) \) is the penalty term (lambda [\lambda]) and the solution is identical to OLSLR when \( \lambda P_\lambda(\beta) = 0 \). A large lambda value will result in a large number of variables in the final model; however, prediction accuracy can be large or small. The lambda value is selected by yielding the minimum squared error in leave-one-out cross validation; thus, data from a single eye were used as a testing dataset and all other data were used as training data. This procedure was repeated so that each eye was used only once as testing data. In other words, for each eye, the TD value at each VF test point was predicted using the 513-cpRNFL thickness values from all other eyes (186 eyes), and the lambda value minimizing prediction error was identified.

Ridge regression is similar to LASSO regression, but different in that the penalty term \( \lambda P_\lambda(\beta) \) (L1 normalization) is replaced by a penalty term of \( |\beta_j|^2 \) (L2 normalization). In the current study, we chose LASSO regression, not ridge regression, because LASSO regression usually yields more accurate predictions than ridge regression, unless coefficients for all variables are roughly of equal size.13 LASSO regression also has an advantage over ridge regression in that the final model may...
involve only a subset of the predictors, which, in turn, improves model interpretability.

The optic disc angle corresponding to each of the 10-2 HFA VF test locations was determined by multiplying the angle of cpRNFL thickness (from $90^\circ$ to $360^\circ$) and the coefficients of the cpRNFL thickness LASSO regression (see Fig. 1).

All statistical analyses were carried out using the statistical programming language R (ver. 3.1.3; The R Foundation for Statistical Computing, Vienna, Austria).

**RESULTS**

Subject demographics are summarized in the Table. Mean ± SD age was 55.8 ± 16.1 years, and the same statistics for mean deviation (MD) were −8.51 ± 9.12 dB.

Figure 1 shows the calculation of the optic disc angle for a sample VF test point. In this example, the optimal LASSO regression formula between the TD value and cpRNFL thickness was $TD = -35.4 + (0.088 \times \text{cpRNFL}_{90}) + (0.025 \times \text{cpRNFL}_{-90}) + (0.078 \times \text{cpRNFL}_{70}) + (0.0051 \times \text{cpRNFL}_{-70}) + (0.017 \times \text{cpRNFL}_{30}) + (0.030 \times \text{cpRNFL}_{-30}) + (0.028 \times \text{cpRNFL}_{30})$, and the optic disc angle corresponding to the VF test point was calculated as: $(0.088 \times -90 + 0.025 \times -89.6 + 0.078 \times -70.0 + 0.0051 \times -67.5 + 0.017 \times -39.7 + 0.030 \times -38.7 + 0.028 \times -38.7) / (0.088 + 0.025 + 0.078 + 0.0051 + 0.017 + 0.030 + 0.028) = -69.6^\circ$.

The results are shown using 15 sectors proposed by Wirtschafter et al.\(^1\) in Figures 2A and 2B, for the purpose of interpretation in the figures. In addition, the results presented here are consistent with the mapping reported by Hood et al.\(^1\); in particular, superior central VF test points as shown by Hood et al.\(^1\) in Figure 2C to help interpret the results considering the relation between retinal ganglion cell locations and VF test points. In general, the results presented here are consistent with the mapping reported by Hood et al.\(^1\).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age, y (mean ± SD) [range]</td>
<td>Total 55.8 ± 16.1 [23.0–87.9]</td>
</tr>
<tr>
<td></td>
<td>POAG 62.1 ± 10.1 [26.0–87.0]</td>
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<td></td>
<td>Healthy 28.9 ± 6.27 [23.0–48.0]</td>
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<td>Sex (male/female)</td>
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<td>Eyes (right/left)</td>
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<td></td>
<td>POAG 73/78</td>
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<tr>
<td></td>
<td>Healthy 22/15</td>
</tr>
<tr>
<td>Axial length, mm (mean ± SD) [range]</td>
<td>Total 24.6 ± 0.95 [22.0–26.0]</td>
</tr>
<tr>
<td></td>
<td>POAG 24.6 ± 0.94 [22.0–26.0]</td>
</tr>
<tr>
<td></td>
<td>Healthy 24.4 ± 0.96 [22.4–26.0]</td>
</tr>
<tr>
<td>MD, dB, (mean ± SD) [range]</td>
<td>Total −8.51 ± 9.12 [−31.5 to 1.97]</td>
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<tr>
<td></td>
<td>POAG −10.4 ± 5.33 [−31.5 to 1.97]</td>
</tr>
<tr>
<td></td>
<td>Healthy −0.26 ± 0.92 [−2.15 to 1.33]</td>
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correspond to a more vulnerable area of the optic disc more distant toward the inferior pole from the center of the temporal quadrant (9:00 o’clock for the right eye) while inferior VF test points correspond closer to the center of the temporal quadrant. More specifically, less vulnerable areas correspond to sectors 1, 2, 3, 4, and 15 and more vulnerable areas correspond to sectors 12, 13, and 14.

Figure 3 shows the values of lambda describing the optimal structure–function relationship at each test point. In general, lambda values are smaller in the central area, suggesting a stronger relationship between the TD value and cpRNFL thickness.

Figure 4 shows the correlation between each of cpRNFL thickness (1024 points) and TD values at each test point on the 10-2 HFA VF, following the study by Gardiner et al. In general, the results were consistent with the results shown in Figures 2 and 3; the angles shown in Figure 2 had strong correlation in Figure 4, and also the correlation in Figure 4 was weak in the least vulnerable area, whereas opposite tendency was observed in the more vulnerable area (both in Figs. 3, 4).

Figure 5 shows the relationship between the values of lambda and mean predicted visual sensitivity. There was a significant relationship between these values (correlation coefficient = −0.60, P < 0.01).
Figure 6 shows the absolute prediction error (Fig. 6A, left panel), Pearson’s correlation coefficient between the predicted TD value and actual TD value (Fig. 6B, middle panel), and the mean and SD values of actual TD value (Fig 6C, right panel), at each test point. In general, there was a tendency for the absolute prediction error and SD of the TD values to be large in the more vulnerable area; however, the correlation coefficients between the predicted TD values and actual TD values were high in the more vulnerable area.

**DISCUSSION**

In the current study the relationship between cpRNFL thickness and 10-2 HFA VF sensitivity (TD value) was analyzed using LASSO regression, in 151 eyes of 151 POAG patients and 35 eyes from 35 healthy eyes. As a result, it was suggested that the superior central VF corresponds to the area of the optic disc toward the inferior pole from the center of the temporal quadrant (9:00 o’clock for the right eye) while the inferior VF corresponds closer to the center of the temporal quadrant. In the paper by Hood et al., the RNFL stream was traced and the corresponding angle on the optic disc was identified. In general, the current mapping was consistent with that reported by Hood et al. In particular, a more vulnerable region of the optic nerve head (between 40° and 67.5° inferior...
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**FIELD VIEW**

<table>
<thead>
<tr>
<th>Field View</th>
<th>A: Absolute prediction error mean (SD)</th>
<th>B: Pearson's correlation coefficient between predicted and actual TD values</th>
<th>C: Mean and SD values of the actual TD value mean (SD)</th>
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<td>8.7 (3.3) 8.4 (3.2)</td>
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<td>0.79 (0.77)</td>
<td>-127 (12.3)</td>
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<td>8.2 (3.2) 8.1 8.5</td>
<td>0.78 (0.80)</td>
<td>-117 (12.3)</td>
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<td>0.79 (0.79)</td>
<td>-129 (12.8)</td>
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<td>0.79 (0.79)</td>
<td>-128 (12.1)</td>
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<td>0.74 (0.72)</td>
<td>-122 (14.0)</td>
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<td>6.7 (3.2) 7.1 8.5</td>
<td>0.72 (0.74)</td>
<td>-121 (13.0)</td>
</tr>
<tr>
<td></td>
<td>6.7 7.1 8.5 (3.2)</td>
<td>0.72 (0.74)</td>
<td>-118 (12.7)</td>
</tr>
<tr>
<td></td>
<td>6.4 (3.2) 6.7 7.1</td>
<td>0.77 (0.76)</td>
<td>-119 (12.7)</td>
</tr>
<tr>
<td></td>
<td>6.4 6.7 7.1 (3.2)</td>
<td>0.75 (0.76)</td>
<td>-118 (12.7)</td>
</tr>
</tbody>
</table>

**FIGURE 6.** The absolute prediction error, the correlation coefficient between the predicted TD values and actual TD values, and the mean and SD values of the actual TD value, at each test point. (A) Absolute prediction error, (B) Pearson's correlation coefficient between the predicted TD values and the actual TD values, and (C) mean and SD values of the actual TD value, at each test point.

The lambda values in Figure 3 represent the penalty terms in the best-fitting LASSO regression models for each test point's structure–function relationship. As shown in Figures 3 and 4, lambda values tended to be smaller in the central area, which closely matches the area identified as least vulnerable in Hood et al.11 (the temporal area on the optic disc). In the current study, the relationship between the magnitude of lambda and predicted sensitivity was significant: lambda values tended to be large where predicted visual sensitivity was low (Fig. 5). More specifically, as shown in Figure 6, the absolute prediction error tended to be large in the more vulnerable area where the lambda value was large. This may be because the region of RNFL that corresponds to these field locations is inherently more vulnerable, so a wider region of RNFL is used in the predictions to 'smooth out' this variability. This raises a question about the usefulness of the proposed LASSO prediction model in areas where lambda is large. However, the correlation coefficients between the predicted TD values and actual TD values were high in this area. Further, as shown in Figure 6, the SD values of the TD values in this area were high compared with those in the least vulnerable area; thus, the predicted TD value was more variable in the more vulnerable area, compared with those in the least vulnerable area. However, as discussed, the larger absolute prediction error in the more vulnerable area may simply be inherited from the inherently larger variability of TD values in this region.

A limitation of the current study was that myopic eyes were excluded. As noted above, the structure–function mapping can change with an increase in axial length5,24, hence, a further study in myopic eyes is needed to shed light on this issue.

In conclusion, a structure–function map was obtained for the central 10° VF based on the strength of the structure–function relationship. The mapping was, in general, consistent with the mapping reported by Hood et al.11

**Acknowledgments**

Supported in part by the Japan Science and Technology Agency (JST)-CREST JPMJCR1304 and Grant 17K11418 from the Ministry...
of Education, Culture, Sports, Science and Technology, Tokyo, Japan.

Disclosure: Y. Fujino, None; H. Murata, None; M. Matsuura, None; M. Yanagisawa, None; N. Shoji, None; K. Inoue, None; J. Yamagami, None; R. Asaoka, None

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