Deriving visual field loss based upon OCT of inner retinal thicknesses of the macula

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Abstract: Using a multiple linear regression method, a derived visual field (VF) was obtained from retinal ganglion cell and retinal nerve fiber layer (RNFL) thicknesses measured with frequency-domain, optical coherence tomography (OCT) macular scans. 138 eyes from 92 glaucoma patients or suspects and 58 healthy eyes were included. The derived VF was compared to the VF measured with standard automated perimetry (SAP). The median agreement between the derived and observed VFs was 90%. As the derived and observed VFs should be independent, they can be combined to potentially increase the sensitivity/specificity of a test for glaucoma.

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OCIS codes: (170.4500) Optical coherence tomography; (330.4300) Vision system—noninvasive assessment

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1. Introduction

Clinically, glaucomatous damage is typically diagnosed via a combination of structural and functional measures. In particular, a loss of visual field (VF) sensitivity as measured with standard automated perimetry (SAP) is compared to structural/anatomical damage. While earlier work focused on structural damage to the optic nerve head (ONH) as viewed on fundus photographs, the advent of imaging technologies such as scanning laser polarimetry (SLP),
scanning laser ophthalmoscopy (SLO) and optical coherence tomography (OCT) made it possible to obtain topographical information about local damage to the ONH, retinal ganglion cells (RGCs) and retinal nerve fiber layer (RNFL). It is clear that the clinician is aided by having both structural and functional measures. However, it is less clear how best to combine information from the functional SAP tests and structural OCT measures. Here we are interested in deriving losses in SAP sensitivity from OCT images so that these derived SAP values can be compared to those directly measured.

One approach to studying the relationship between imaging and SAP data is the direct correlation method, where a retinal image, typically the image around the optic disc, is divided into discrete sectors and correlated with the loss in local VF sensitivity. For example, Gardiner et al. [1] used this method on ONH images and VFs from patients with glaucoma to relate regions on the VF to locations at the optic disc. As they point out, the uncertainty in these maps is in part due to the covariance among locations in the retinal image. As a consequence, the RNFL thickness measure from one retinal location can be positively correlated with a VF location that has no anatomical connection with it. To address this challenge, Zhu et al. [2] used a neural network approach to analyze RNFL data from SLP disc scans. They found that this method was superior to a multiple linear regression (MLR) method.

However, there is a challenge associated with any attempt to predict the VFs using thickness measures from only optic disc scans. Any part of the RNFL consists of axons originating from all RGCs along the same arcuate path in the retina. For example, consider two retinal locations, A and B, along an arcuate, where A is closer to the ONH. The RNFL at A (RNFL\textsubscript{A}) contains axons that originate from B as well as those which originated from A. As arcuate defects frequently occur in glaucoma patients, the visual field sensitivity at A (VF\textsubscript{A}) and at B (VF\textsubscript{B}) often will be decreased concurrently, thus resulting in a positive correlation between RNFL\textsubscript{A} and VF\textsubscript{B}, even though the damage of RGC\textsubscript{A} alone should not affect VF\textsubscript{B}. If point B is outside the region examined by the disc scan, it is impossible to distinguish between loss at VF\textsubscript{A} and VF\textsubscript{B} with the disc image. Technically, when we rely on the thickness of the RNFL at the optic disc to predict VF sensitivities, a 1-dimensional set of data is used to predict a 2-dimensional one. For the RNFL of the disc scan, there is only one degree of freedom, namely the clock hour around the disc. On the other hand, the VF is a 2-dimensional data set.

This problem can be avoided by studying the macular region, which extends to a visual angle of about 10° around the fovea. Our interest in the macula stems from its paramount importance in visual function. However, by studying the macula we can also meet the challenge described above. In particular, by using a macular cube scan as our OCT measure and a VF that covers the central 10°, our OCT and VF measures are coextensive in 2 dimensions. Further, because of the thickness of the OCT RGC layer in the macula, we can obtain good measures of both the RNFL and RGC in this region. In short, the use of macular OCT images not only allows us to investigate the structure-function relationship in the important macular region but also allows us to effectively apply MLR to derive the topographical relationship between the VF fields and OCT images.

2. Materials and Methods

2.1. Subjects

This study included 138 eyes from 92 patients (59 ± 11 yrs) and 58 normal eyes from 38 control subjects (42 ± 18 yrs). All subjects had fOCT scans and the patients had 10-2 VFs as well. The patient had glaucomatous optic neuropathy with (glaucoma) or without (suspects) abnormal 24-2 VFs. The mean pattern standard deviation (PSD) of the 10-2 VF was −3.6 dB with a [5%; 95%] interval of [−14.6 dB; −0.93 dB]. To be included, the VF of glaucoma eyes...
had to be reliable (indices <30%). The controls had normal vision, no history of elevated intraocular pressure, and a normal optic disc appearance.

Written, informed consent was obtained from all participants. Procedures followed the tenets of the Declaration of Helsinki and the protocol was approved by the Institutional Review Boards of Columbia University and New York Eye and Ear Infirmary.

2.2. RGC + IPL and RNFL thicknesses and visual field measures

On many scans, it was not possible to reliably distinguish the RGC layer from the inner plexiform layer (IPL). Thus, the thickness of the combined RGC and IPL was measured and referred to as RGC + IPL. The RGC + IPL and RNFL thicknesses were measured using fdOCT (3D-OCT 2000/1000; Topcon, Inc., Oakland, NJ) and a 6 mm × 6 mm macular cube scan. The layers of retinal structures were segmented with an automated segmentation algorithm [3]. Individual scans were inspected by eye to remove the scans with acquisition/algorithm failures. Figures 1B-D show three B-scans from a typical OCT macular scan. The red, yellow and green lines show the algorithm segmented borders used in this study. From the top of each panel, these lines are the: vitreous/RNFL (green), RNFL/RGC (red), and IPL/inner nuclear layer (yellow) borders. Thus, the green and red line and the red and yellow lines demarcate the RNFL and the RGC + IPL layer, respectively. The thicknesses of these two layers were determined from these segmented borders. The OCT images have a resolution of 512 × 128, but this was reduced to 64 × 64 to decrease the memory demand for computation.

Fig. 1. The OCT macular cube scan. A. Fundus picture showing extent of cube scan and the location of the line scans in panels B-D. B-D. The results of the automatic segmentation for the locations indicated in panel A. The vitreous/RNFL (green), RGC/RNFL (red) and IPL/inner nuclear layer borders are shown.

The pattern deviation values of the VF, obtained with 10-2 white-on-white SAP (Carl Zeiss Meditec, Inc., Dublin, CA), were used for this analysis. (Similar results were obtained with the total deviation values.) At each location of the field, if the value of the patient’s VF was larger than 0 dB (more sensitive than normal), the value was set to 0 dB. Because the VF data were not available for all the normal eyes, the value of VF was set to 0 dB for all locations of all the control fields. For all eyes, the data from left eyes were flipped to coincide with those of a right eye.
2.3. The multiple linear regression (MLR) method

2.3.1. Multiple linear regressions

MLR is a natural extension of the more familiar one-dimensional linear regression, in which the dependent variable is derived from the independent variable based on samples of both variables. MLR allows any of the independent variables to predict any of the dependent variables. In other words, in principle, any point of the OCT image can be correlated with any of the test points on the VF. This allows both for the well-known displacement of the RGCs away from location that the light from the VF test falls [4,5], and for the fact that the RNFL thickness at any given point is not necessarily correlated with the underlying RGC thickness at that point.

2.3.2. Principal component analysis

For the MLR method, the number of independent variables has to be smaller than the size of the data. The RNFL and the RGC + IPL images were decomposed into principal components (PCs) with a principal component analysis (PCA). In this way, the OCT data for all the eyes were transformed into PCs, which are mutually independent of each other. One should think of the PCs as accounting for the variance in the data; the first PC accounts for the greatest variance in the data, while the second the greatest variance after the first PC has been removed, and so on. As a result, each successive PC contributes less to the composite image since it accounts for less of the variance. Thus the higher-order PCs only represent noise in individual data and can be ignored. In this study, we found that only the first 24 most significant PCs were needed to adequately represent the signal in the OCT data. Therefore, the independent variables in MLR are the 24 PCs derived from the OCT data.

2.3.3. General approach

A leave-one-out approach was used. In particular, for each iteration of the PC analysis, one of the 196 eyes was set to be the test eye and the remaining 195 eyes were used as the sample eyes for building the transformation map between the OCT and the visual field with the MLR analysis. Using a method described in more technical detail below, the RNFL and RGC + IPL images of the test eye were reconstructed (Fig. 3, 2nd column) using the 24 PCs. Assuming a linear relationship between VF loss (in linear terms) and OCT thickness, the derived VF (Fig. 3, 3rd column) was generated. Note that by “OCT thickness” we now mean a linear combination of OCT thicknesses of both the RGC + IPL and RNFL layers. Given previous work supporting this assumption for OCT data [6,7] and imaging data [8,9], it was not surprising that this assumption worked well.

2.3.4. Agreement between derived and measured VF

We called a visual field point abnormal if its value was less than $-5$ dB on the measured VF. The particular value of this cutoff is not important, but $-5$ dB was chosen as it is approximately the 5% level on the 10-2 VF. To evaluate the accuracy of the derived VF, we set a cutoff for the derived VF ($-3.9$ dB) so that the total number of abnormal visual field points, across all the glaucoma eyes, was the same as for the measured VF. The percentage of points in the two VFs that agreed was taken as the measure of the agreement between the derived and measured VFs.

2.3.5. Mathematical details

Formally, an MLR with a constant offset is a linear map $A$ and a vector $b$ such that if $X$ is the matrix of independent variables, and $Y$ is the matrix of dependent variables

$$
\| (A \times X + b) - Y \| = 0
$$

(1)
where $\|\cdot\|$ denotes the usual Euclidean norm. Equivalently, we may represent the MLR as a single linear transformation $T$ where $T = (A \ b)$, the matrix obtained horizontally concatenating $A$ and $b$. If $X'$ is the matrix formed by appending a row of 1’s to the bottom of the matrix $X$ of independent variables, it follows that

$$
\|T*X' - Y\| = 0 \iff \|(A*X + b) - Y\| = 0
$$

For this study, the MLR method was a three-step process:

1. The data for each sample OCT image, comprising the thicknesses of the RNFL and RCG + IPL, were initially reorganized as a single column vector. The vectors corresponding to each sample eye were then collected into a single matrix $S$ with 195 (the number of sample eyes) columns. After subtracting the mean thicknesses of the sample OCT images from $S$, singular value decomposition was used to obtain the PCs, which are orthonormal (orthogonal and of equal magnitude) as vectors. Thus,

$$
S = M*D*N
$$

where $M$, $N$ are unitary matrices, and $D$ is a diagonal matrix. The columns of $M$ represent the PCs, while the rows of $N$ correspond to the PC coefficients for each sample eye in terms of those PCs, and the entries along the diagonal of $D$ are scaling factors corresponding to each PC. For our purposes, only the first 24 major PCs were used while the other PCs were discarded as they represent individual noise in the data. From here on $S$ will denote the adjusted sample matrix, i.e. the matrix obtained after removing higher-order PCs.

2. Let $S'$ be the matrix obtained from $S$ by adding a row of 1’s, and let $V$ be the matrix of VF's for the sample eyes, with VF sensitivities given in linear values, i.e. $10^{[\text{VF in } \text{DB}]}/10$. In this paper, $V$ consists of 68 rows (the number of 10-2 VF points) and 195 columns. Following the discussion above, the MLR between the sample OCT images and their VFs will be a matrix $T$ such that $\|T*S' - V\| = 0$. Unfortunately, one cannot expect a solution for $T$ unless there is a perfect linear relationship between $S'$ and $V$. However, one can always find a $T$ such that $\|T*S' - V\|$ is minimized, and such a $T$ is guaranteed if we choose $T = V*MP(S')$, where $MP(S')$ is the Moore-Penrose pseudoinverse of $S'$. $T$ represents our OCT-to-VF transformation.

3. Explicitly, the Moore-Penrose pseudoinverse of a matrix is derived from its PC decomposition. Let $S$, $M$, $D$ and $N$ be as in Eq. (3). Then the Moore-Penrose inverse of $S$ is given by

$$
MP(S) = N^*D^+*M^t
$$

where $M^t$ and $N^t$ are the respective transposes (and hence inverses) of the unitary matrices $M$ and $N$, and $D^+$ is the transpose of the matrix obtained from $D$ by inverting all the entries along the diagonal.

Using a column vector $v$ to represent the test eye’s RGC + IPL and RNFL image with an extra row for the constant term, the weighting for the reconstructed OCT image ($oct$) of the test eye is given by

$$
oct = MP(S')^*v
$$

In essence, $oct$ is obtained by first writing $v$ as a linear combination of the 24 PCs ($M^tv$), and then representing this linear combination as a weighted sum of the PC coefficients for the sample eye OCT images ($(N^*D^+)(M^tv)$). Hence, $oct$ is a $195 \times 1$ column vector of “weights,” corresponding to how much the nth sample eye’s OCT image contributes to reconstructing that of the test eye. Because the Moore-Penrose pseudoinverse minimizes the RMS error between the reconstructed OCT image and the original OCT image, $oct$ is in some
sense the “best approximation” to the test eye’s OCT image when written as a combination of the OCT images of the sample eyes.

The derived VF for the test eye (vf) is then given by

\[ vf = T^*v = (V^*MP(S)^*)^v \]  \hspace{1cm} (6)

By the discussion above, we have equivalently

\[ vf = V^{*\text{oct}} = V^*(MP(S)^*)^v \]  \hspace{1cm} (7)

Thus, by associativity, we can regard the MLR either as an OCT-to-VF map \( T \), as in Eq. (6), or as the weighted sum of sample eye VFs based upon the coefficients for reconstructing OCT image for the test eye, as in Eq. (7).

3. Results

Figure 2 shows the 24 PCs as pairs of RGC + IPL and RNFL thickness images. All images are presented in field view. Red indicates positive and blue color indicates negative thicknesses relative to the mean. (Note that both the sign and the scale of PC images are arbitrary.) While PC images need not correspond directly to known patterns of glaucomatous damage, it is evident from the images in Fig. 2 that at least in some cases they do. For example, PC1 represents the average RGC + IPL and RNFL thicknesses, when there is no glaucomatous damage, and PC2 resembles the superior field arcuate damage.

![Fig. 2. The 24 PCs. The sign and hence the color of the PCs are arbitrary.](image)

Figure 3 shows three typical results. First, note the similarity between the raw OCT data (1st column) and the reconstructed RGC + IPL and RNFL data (2nd column). This similarity indicates that 24 PCs are sufficient to represent the OCT data. The only details lost, such as streaks of artifacts due to blood vessels (black arrow at the bottom of the 1st column), are noise. The third and fourth columns of Fig. 3 show the derived and measured VFs, where the large blue circles are abnormal points as defined in the Methods.
Fig. 3. Three sample results. The raw OCT images (column 1) are shown with the reconstructed images (column 2) derived from the 24 PCs in Fig. 2. The OCT data consist of both RNFL (upper) and the RGC + IPL (lower) thickness images and have been rotated to field view to be consistent with the presentation of VF. From the reconstructed OCT images the derived VF (3rd column) is determined, which can be compared to the measured VF (4th column). The color scale, lower left, is the same for all the OCT images. A blue dot in columns 3 and 4 indicates it is abnormal when compared to healthy controls.

To obtain a quantitative measure of the agreement between the derived and measured VFs, the proportion of the points showing agreement was calculated. Overall, the agreement ranged from 0.51 to 1.00. Figure 3 shows examples where 0.88, 0.96 and 0.60 of the points agreed. The histogram in Fig. 4A shows that for most eyes, the agreement between the measured VF and the derived VF was high. For the 138 patient eyes, the median agreement was 90% and the agreement for 95% of the eyes was greater than 62%.

![Diagram](image)

Fig. 4. A. The histogram for the agreement between the measured VF data vs. the derived VF for 138 glaucoma eyes. B. The coefficient of determination (R²) values between derived VF and the measured VF for 138 glaucoma eyes for all the locations of the VF.
Figure 4B shows that for most locations, the coefficient of determination ($R^2$ values) between the measured and derived VF were reasonably good, especially given the variability inherent in the visual field measures, as well as the variability in retinal anatomy among individuals. The red contour in Fig. 4B shows the region with $R^2$ values less than 0.20. Perhaps not surprisingly, this region, outlined in red, corresponds to the anatomical region least likely to be affected by glaucoma. This is supported by Fig. 5, which shows the scatter plots of derived vs. observed VF for each test field locations. The range of observed VF losses is smaller for those locations with smaller $R^2$.

4. Conclusion

Using the MLR approach described here, a VF can be derived from the OCT thickness data in a few seconds of computer time. Although a RNFL or RGC + IPL thickness image (1st column of Fig. 3) is dramatically different from the measured pattern deviation VF (4th column of Fig. 3), they can be turned into a form that can be directly compared.
It is important to emphasize that we did not expect to find a perfect agreement between the derived and measured VFs; in fact, there are reasons to expect discrepancies. First, both OCT and VF measures are subject to the variability caused by measurement error. Second, there are individual differences in the way the VF points are mapped to both RNFL locations at the optic disc [6,7,10] and RGC densities in the macula. Finally, and perhaps most importantly, the two tests do not measure the same thing. In fact, there is reason to believe that one test or the other might be more sensitive for detecting glaucomatous damage in a particular patient [7]. On the other hand, if there were perfect agreement, functional data would contribute no new information about a subject that could not be gained from structural measurements.

The MLR approach provides more than a way to visually compare OCT and VF data. To a first approximation the sources of error in the derived and measured VFs should be independent. Thus, we should be able to combine probabilities derived from each to increase the sensitivity/specificity of a combined test for glaucoma.

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