Individual Differences in Foveal Shape: Feasibility of Individual Maps Between Structure and Function Within the Macular Region

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PURPOSE. Recently in glaucoma, different mapping schemes to combine structural and functional information within the macula have been proposed. This paper aims to investigate whether the changes in foveal shape parameters are important in the mapping between structure and function within the macular region.

METHODS. Twenty younger adults (aged 24- to 33-years old) and 10 older adults (aged 62- to 76-years old) participated. On each subject, four foveally-centered radial spectral-domain optical coherence tomography (SD-OCT) scans with 45° of separation between each scan were acquired. After scan acquisition, foveal shape was extracted by fitting a previously proposed model that has been used to customize structure-function mapping in the macular region. Three parameters were obtained from the scans and then compared: the central thickness, the maximum thickness, and the radius.

RESULTS. There were significant differences in the foveal shape parameters between subjects. There was no main effect of the scan axis for the central thickness; however, there was an interaction between the scan axis and maximum thickness and between the scan axis and radius. With respect to the effect of age, we did not find a main effect for the central thickness, the maximum thickness or the radius, although this parameter approached statistical significance.

CONCLUSIONS. In our study, we demonstrated that the foveal shape is different for different subjects, but predictable superiorly and inferiorly within an individual. Our study highlights features important for the development of individually customized structure-function maps for the investigation of glaucomatous damage in the macular region.

Keywords: macular, structure-function, foveal shape

There is recent, increased interest in the macula region in glaucoma, both for structural and functional assessments. In order to combine information from the two, a mapping schema is required. In the macular region the retinal ganglion cells do not lie directly above their photoreceptors, but are displaced away from the fovea by a distance commensurate with Henle fiber length in order to maintain excellent foveal acuity. Hence, there is a displacement between the location of visual field stimulation and the relevant spatial region of the macular optical coherence tomography (OCT) scans.

Several studies have approached this problem by using the mapping schema suggested by Drasdo et al., which describes the on-average displacement of the ganglion cells from their photoreceptors according to the Henle fiber length. For instance some authors reported that after considering this “on average” ganglion cell displacement in the macula, the sectoral structure-function relationship in glaucoma improves, especially within the central 10° of the visual field. More recently, Turpin et al. have published a method for customizing such mapping based on an individual person’s retinal ganglion cell plus inner plexiform layers (RGC+IPL) profiles obtained from macular OCT scans.

The customized mapping approach within the macular region relies on an estimate of RGC density obtained from OCT scans of healthy, baseline retina. In glaucoma, macular OCT deficits are often asymmetrical relative to some approximately horizontal midline, thus there are two choices of mapping schemes if damage is present: (1) choose the population average mapping as per Drasdo, or (2) estimate RGC density for the whole macular based on scans in “normal” regions of the macula. For option 2 to be useful, there needs to be a predictable relationship between macular shape along many different meridians in the retina, thus allowing estimation of the baseline RGC density in damaged regions from the still normal regions.

The broad purpose of this study, therefore, was to investigate factors that are important to determining whether customizing structure-function mapping within the macular region is likely to yield clinical benefit. As the locations in the retina at which the mapping might be required depends on the visual field test pattern used to collect functional information, any mapping scheme should work across the whole macular, and not just along b-scan lines of the OCT used to collect structural information. Furthermore, such a mapping might require the foveal shape at many eccentricities, and not just at a
handful of points that could be manually measured (for example, using OCT calipers by a human grader). To meet these requirements, we describe the foveal shape using a mathematic method that is automatically derived from OCT b-scans. In turn, foveal shape parameters can be extracted from this model and applied to a customized macular mapping approach as described in Turpin et al. that is independent of the type of OCT device used.

A number of previous studies have reported individual variation of the foveal shape, however these previous studies considered the direct measurements of the foveal shape parameters and did not consider the specific factors that are relevant to glaucomatous structure-function mapping. Our experiments extend on these previous works and address the following three primary aims: (1) to determine the level of interindividual differences in foveal shape in young normal observers for the specific parameters that are important for customizing structure–function mapping across the macula, (2) to determine the level of symmetry in foveal shape and whether it is possible to predict the superior foveal parameters from the inferior parameters in young eyes where there is no expected loss to due age or disease, and (3) to explore whether the foveal shape parameters as measured by the model of macula shape described by Scheibe et al. vary between older and younger adults. An additional aim of the project was to report the test-retest variability of the foveal shape parameters measured using the Spectralis spectral-domain OCT (SD-OCT; Heidelberg Engineering, Heidelberg, Germany), in order to determine whether multiple measures are required in a clinical setting to provide a reliable estimate of foveal shape.

**Methods**

**Participants**

Twenty healthy, young participants (7 male, 13 females), aged 24- to 33-years old (median = 28), and 10 healthy, older participants (4 male, 6 female), aged 62 to 76-years old (median = 69) were tested. For each participant only one eye was randomly selected (15 right eye, 15 left eye). Younger controls were recruited from the staff, students, or personal contacts from the Department of Optometry and Vision Sciences at the University of Melbourne (Melbourne, Australia). Older controls were recruited from a database of volunteers from other studies performed within the laboratory of the investigators.

All of the participants were screened in a short evaluation consisting of clinical history questions, best-corrected visual acuity and refractive error measurement, slit-lamp examination, measurement of the pupil size in light conditions, and Amsler grid testing. All of the selected participants had a refractive error lower than ±6 diopters (D) spherical and/or −2 D cylindrical (mean spherical equivalent younger adults: −1.4 D, SD = 1.63; mean spherical equivalent older adults: −0.2 D, SD = 1.05; t(25.9) = −3.5, P < 0.01), a pupil size higher than 3 mm and none of them presented any important systemic or ophthalmic disorder (such as maculopathy, important media opacities, or fixation problems). Refractive errors and axial lengths for each participant are given in Supplementary Table.

All of the procedures conformed with the tenets of the Declaration of Helsinki. This project was approved by the University of Melbourne Human Research Ethics Committee (HREC 1238744), and all the individuals provided written informed consent.

**OCT Imaging**

Optical coherence tomography scans were acquired using the Spectralis SD-OCT with a customized high-resolution radial scan centered automatically on the fovea according to subject fixation. Four slices with an angular separation of 45° each were taken (Fig. 1, left panel). Images were acquired using the automatic real time mean (ART) function of the Spectralis in order to obtain the maximum resolution averaging 100 frames. This allows an image resolution of 3.87-μm axial, 11.2-μm transverse, and 1.9-μm of penetration. We used high-resolution radial scans rather than cube-volume scans of the macula to avoid differences in the data resolution across different meridia.

After the image acquisition, the operator (JS) proceeded to verify the image quality, choosing those with a signal higher than 15 dB. The Spectralis SD-OCT provided automatic segmentation of the inner limiting membrane (ILM) and Bruch’s membrane (BM) boundaries (Fig. 1, right panel). All images were inspected for segmentation accuracy of these boundaries (JS), with the intent of manual correction if required. For these boundaries (ILM and BM) the automated segmentation algorithm of the Spectralis was deemed accurate for all images. The processed images were later exported to a .vol file and analyzed using a custom software written in R version 3.1.1.

**Foveal Shape Model**

The majority of previous studies performed to determine individual variability in foveal shape have used direct measurement obtained from OCT devices. In our study, we used a fitted mathematical model proposed by Scheibe et al. to the images because being able to determine shape at many different locations across the whole macular is important for structure–function mapping. In our previous study, we used the same model to estimate the shape of the GCL+IPL for the...
purpose of customized structure–function mapping in the macula. Briefly, the model is “one-sided,” modelling a curve from the fovea out to the more peripheral retina as the sum of two exponential functions. The first function has three parameters that control the location, height, and steepness of the rim. The second function makes use of the width and steepness parameters, and has a fourth weighting parameter that is the height of the retina outside the fovea. By fitting these four parameters to minimize the sum-of-square differences between the function and one-half of the OCT profile, one has a simple formula that describes the profile, allows easy extraction of measurements, and can be readily interpolated to other meridians of the macula. Figure 2C shows an example of the fitted model.

In this paper, we are interested in the total foveal shape profile, so we fit the model to the entire retinal thickness profile, not just the GCL+IPL. To obtain this total foveal shape profile, from the Spectralis .vol file we subtracted the ILM profile as segmented by the Spectralis software from the RPE profile as given by the Spectralis. After obtaining this total retinal profile, the point of minimum thickness was calculated by scanning from the left and right while the difference is decreasing, and taking the minimum of the two. This point was considered as the center of the scan. This process is shown in Figure 2, where the ILM and RPE are taken from Figure 1 (Fig. 2A), the difference taken (Fig. 2B), and the minimum of that difference used to find the midpoint of the scan (Fig. 2B). The scan was divided in two, and the four-parameter Scheibe model fitted to each half (Fig. 2C). While this fitted curve is important for structure–function modelling, in this paper we are interested in three measurements: the central thickness (an estimate of the ILM-RPE difference at the point of minimum thickness; Fig. 2A), the maximum thickness (an estimate of the IPL-RPE difference at its highest computed as “Height” in Fig. 2C plus “Central thickness” from Fig. 2A), and the radius, corresponding to the distance between the center of the scan and the point of the maximum thickness (Fig. 2C).

Statistical Analysis

Statistical analysis was performed using SPSS Statistics for Windows, Version 20 (IBM, Chicago, IL, USA). In this study, $P$ less than 0.05 was set as a level of statistical significance. Graphs were plotted using R Version 3.1.1. For the purposes of analysis, the axis from the fovea to the optic disc was labelled as $0^\circ$, with angles increasing to the superior $90^\circ$ and around to the inferior $270^\circ$.

RESULTS

Between-Subjects Differences

In order to verify that the foveal shape differs between individuals, we calculated the population 95% confidence intervals for the central thickness, the maximum thickness, and the radius for the 30 healthy subjects for each retinal meridian

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<th>Axis</th>
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* These values are the same as their counterparts less $180^\circ$ because the same scan center was used (i.e., $0^\circ$ and $180^\circ$).
Individual Differences in Foveal Shape

FIGURE 3. The maximum thickness and the radius of the superior (45°, 90°, and 135°) and inferior (225°, 270°, and 315°) meridians were compared using a post hoc Bonferroni comparison. The right side shows pairs of meridians with a statistically significant difference. Note comparisons were only performed across hemifields (superior and inferior), not within hemifields.

tested. Table 1 summarizes the obtained results from the population data, which was calculated parametrically from 1.96 SD of the mean.

Within-Subjects Differences

The central thickness, the maximum thickness, and the radius were compared within the same individuals along different scan axes using a repeated-measures ANOVA. As should be expected, there was no main effect of the scan axis in the central thickness \( F(2.2,63.5) = 1.29, P = 0.28 \) because the point where central thickness was measured was very similar (but not quite identical) for all the scans within an individual. However, there was an interaction between scan axis and maximum thickness \( F(2.57,8) = 28.66, P < 0.01, \) and between scan axis and radius \( F(2.7,79.2) = 21.75, P < 0.01 \).

To determine the specific scan axes that differed in maximum thickness and in radius across the superior and inferior hemifields, a post hoc Bonferroni comparison was performed. The results of the post hoc analysis are illustrated in Figure 3.

Figure 3 shows that the superior and inferior hemifield foveal shapes differ quantitatively, however for the purpose of the structure–function mapping it is sufficient if they are predictable from one another. Hence, we performed a correlational analysis for the maximum thickness and the radius between the superior vertical meridian (90°) and the inferior vertical meridian (270°). We did not consider the central thickness for this analysis because it did not differ between meridians. Our results showed a high correlation between superior and inferior retinal meridians for the maximum height \( r = 0.96 \) younger, \( r = 0.89 \) older, but a weaker correlation for the radius \( r = 0.42 \) younger, \( r = 0.66 \) older; Fig. 4).

Foveal Shape Parameters and Age

A multifactorial ANOVA was applied to determine whether the mean foveal shape parameters for the older eyes differed from those of the younger eyes. The same parameters were compared as in the previous sections (central thickness, maximum thickness, and radius) along the different retinal meridians.

We did not find a main effect of age for the central thickness \( F(2.3,64) = 0.17, P = 0.88 \), maximum thickness \( F(3.5,99) = 1.79, P = 0.15 \) nor for the radius, although this approached statistical significance \( F(4,2,117.7) = 2.37, P = 0.05 \). Figure 5 plots the range of values (1.96 SD from the mean) obtained for the radius within the two age groups for each of the meridian, where it can be seen that there is a trend for a shorter radius in the older eyes, however substantial overlap between the groups.

Test–Retest Variation of the Foveal Shape Parameters

As the measurement conditions can vary during clinical examination (head position, eye fixation, micro saccades), we wanted to know the level of reproducibility of the foveal shape estimates obtained using our methods. We tested five normal younger subjects performing five times within the same session using the cross scan pattern previously described in the methods section. The session did not last longer than 10 minutes, allowing the subject to take a short rest between each scan. Between each scan, the observer sat back and was then realigned, however, we did not turn off the ART function of the Spectralis as this is commonly clinically employed. To determine the test–retest variability of the values obtained, we calculated the coefficient of variation (that is the SD divided by the mean) for the central thickness, the maximum thickness, and the radius. The use of the coefficient of variation allows us to determine the degree of dispersion of the values. Results are shown in Figure 6 and in Table 2. The radius was the most variable parameter.

Role of Axial Length

In order to determine whether the axial length influences the foveal shape, we calculated a correlation between the mean
value of each parameter for each participant and the axial length. We performed this analysis differentiating between younger and older participants. There were no statistically significant relationships between any of the macular shape parameters and the axial length for either age group (Table 3).

**DISCUSSION**

In this study, we demonstrated that there are differences between people in the central thickness, the maximum thickness, and in the radius of the macular shape model, which is consistent with previous reports that showed differences in foveal shape between individuals.\textsuperscript{14–16} The main difference between the current approach and previous approaches is the use of a mathematical model of the foveal shape\textsuperscript{11} instead of the direct measurement using the OCT devices, and the specific comparison of features important for the analysis of glaucomatous damage in the macular (namely superior and inferior hemifield asymmetry).

Typically, OCT devices provide the central thickness values but neither the maximum height nor radius. To obtain these values, a manual approach is to use the calipers provided by the machine, or to use a photo editor software; both of the options operator-dependent and time-consuming to perform across multiple scan meridia. In our study, we obtained the macular parameters using an automated approach by fitting the model of Scheibe et al.\textsuperscript{11} which, according to the authors,\textsuperscript{11} offers high accuracy for describing the foveal shape derived from OCT images. Therefore, our approach offers a less operator-dependent measurement of the three different parameters and is significantly more efficient for implementing across large numbers of images and scan axes.

A key aim of our study was to determine the within subject variability between the superior and inferior macula. The results showed that foveal shape is not symmetrical, with statistically significant differences between some superior and inferior meridia, however a reasonable degree of predictability was observed between the inferior and superior scan axis within individuals (see correlations illustrated in Fig. 4). The intrasubject variability of the macular shape is important because commonly in glaucoma one of the hemifields is more affected than the other. For the purposes of developing individualized structure–function mapping in the macular area, it is important to know if it is possible to estimate one meridian from the other in order to use the shape of the “normal side” to estimate the foveal shape prior to disease of the diseased side in patients with asymmetric macular involvement. Superior and inferior meridians were highly correlated for the maximum thickness, but not for the radius. A likely explanation is the higher measurement variability of the radius (Fig. 6), however it is not immediately clear why the radius was more susceptible to variability. We hypothesize that this variability of the radius may be related with a possible scan tilting or a change of the scan focus after repositioning the patient in the device, although all care was taken to minimize this issue.

In this paper, we used whole retinal thickness as the focus for our exploration of macular shape in people with healthy, normal vision. We chose to study whole retinal thickness, rather than the thickness of the separate layers, because in this study we are interested in whether the general shape of the foveal pit and macular area is variable, symmetrical, and alters with age. The ILM and RPE are easy to segment, and hence lend themselves to automated image processing. However, for the purpose of detailed investigation of eyes with glaucoma, a more layered approach may have some benefits. For instance, Curcio and Allen\textsuperscript{21} reported that the ganglion cell topography varies along the different retinal meridians; however, other

![Figure 5](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/Journals/IOVS/935707/)

**Figure 5.** Ninety-five percent confidence intervals for the radius in younger (blue) and older (green) controls along different axes. Values are represented in microns, and the black lines represent the mean.

![Figure 6](http://iovs.arvojournals.org/pdfaccess.ashx?url=/data/Journals/IOVS/935707/)

**Figure 6.** Coefficient of variation (in percentage) of foveal parameters in the five subjects consecutively tested with the Spectralis SDOCT.
work noted that the ganglion cell topography only contributes in a small proportion to the total macular shape. In glaucoma, outer retinal changes such as photoreceptor swelling may also occur additionally contributing to differences in whole retinal thickness. Note however, that the main purpose of our study is to determine whether macular shape varies sufficiently between normal individuals to warrant customized mapping between structure and function in the macular area. Such customized mapping for an individual likely needs to be established while the individual is a glaucoma suspect to enable careful customized monitoring for future change. Once advanced RGC damage or outer retinal damage has occurred, such fine-scale mapping is unlikely to be accurate or necessary.

We also wanted to verify whether older subjects exhibit similar foveal shape as younger subjects. According to the literature, the aged retina exhibits important changes such as neuronal cell loss, changes in glial supportive tissue, and structural reorganization of the retinal layers. Furthermore, it has been reported that aged fovea are more asymmetric than younger fovea. In the present study, we found that none of the three measured parameters were affected by ageing, however, the radius showed a tendency to be shorter in older participants. Older eyes have been reported to have a sharper slope, however a preserved total volume has been reported. This finding is consistent with our results because a reduced radius with a preserved maximum thickness implies a steeper slope in the foveal shape. Our data does not support the hypothesis that the foveal shape is altered by normal ageing process in retinal structure is highly relevant to studies of glaucoma as it affects mainly older adults; hence, further research to address this important point is warranted with large sample sizes.

Finally, an important point to consider is the reproducibility of tests using the Spectralis. Our results showed that the Spectralis offers high measurement reproducibility, especially for the central thickness and the maximum thickness. Although the radius was the more variable parameter, the coefficient of variation was not high, ranging between 6.26% and 13.04%. As mentioned earlier, perhaps this reproducibility could be improved by better alignment of the scans, however, our scans were taken in a fashion typical of a careful clinical operator in practice. A limitation is that we only measured reproducibility in five subjects as this was not a key focus of our paper. In contrast, a previous work reported a mean of intertest variability in 12 normal subjects of 0.6%, however that study only considered the intertest variability of the central thickness (~6% in our study). While the precision of test–retest will vary between operators and cannot be considered to be definitively quantitatively described by our study, the results highlight that the Spectralis is not free of possible measurement errors, including those that are operator dependent.

In summary, this study demonstrated that the foveal shape is different for different subjects, therefore, the development of an individualized structure–function map for the central 10° in glaucoma is not only feasible but may also be necessary to optimize the mapping between structure and function.

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**References**


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