The proportion of individuals likely to benefit from customized optic nerve head structure-function mapping.

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Financial Support: Australian Research Council Linkage Project 130100055 (industry partner, Heidelberg Engineering, GmBH, Germany). The funding organisation had no role in the design or conduct of this research.

Conflict of Interest: Attached forms for each author

Running Head: Who benefits from individualised structure-function mapping?

Abstract:

Purpose: Inter-individual variance in optic nerve head (ONH) position, axial length and location of the temporal raphe suggest that customizing mapping between visual field locations and optic nerve head sectors for individuals may be clinically useful. Here we quantify the proportion of the population predicted to have structure-function mappings that markedly deviate from "average", and thus would benefit from customized mapping.

Design: Database study and case report

Participants: Population database of 2836 eyes from the Beijing Eye Study; single case report of an individual with primary open angle glaucoma

Methods: Using the morphometric fundus data of the Beijing Eye Study on 2836 eyes and applying a recently developed model based on axial length and ONH position relative to the fovea, we determined for each measurement location in the 24-2 Humphrey visual field the proportion of eyes for which, in the customized approach as compared to the generalized approach, the mapped ONH sector was shifted into a different sector. We determined the proportion of eyes for which the mapped ONH location was shifted by 15°, 30° or 60°.

Main outcome measures: Mapping correspondence between locations in visual field space to localized sectors on the optic nerve head

Results: The largest inter-individual differences in mapping are in the nasal step region where the same visual field location can map to either the superior or inferior ONH depending on other anatomical features. For these visual field locations, approximately 12% of eyes showed a mapping opposite to conventional expectations.

Conclusions: Anatomically customised mapping shifts the map markedly in approximately 12% of the general population in the nasal step region where visual field locations can map to the opposite pole of the ONH than conventionally considered. Early glaucomatous damage commonly affects this

region, hence individually matching structure to function may prove clinically useful for the diagnosis and monitoring of progression within individuals.

Introduction

Both anatomical and functional measures are key to contemporary glaucoma diagnosis and management. Typically these are measured separately, hence in order to relate these two different clinical measures intelligently, it is necessary to have a mapping between the structural parameters (for example, the location on the optic nerve head (ONH) or peripapillary retinal nerve fiber (RNF) layer position) and locations in visual space. Different approaches to such mapping have been proposed, including models derived from hand-tracing and visualisation of RNF bundle trajectories,[1, 2] models derived by visualisation of the absence of RNF bundles in established glaucoma using retinal photography,[3] from geometrical principles,[4-6] or from correlations between structural and functional abnormalities in clinical databases.[7, 8] The advent of high resolution ocular imaging with the capacity to readily and quantitatively assess ocular biometric parameters has seen an increased clinical and scientific interest in the inter-individual differences in key ocular anatomical parameters that are considered to contribute to this mapping.[2, 9-11]

There are several key anatomical features that influence the mapping between structure and function in glaucoma. These include: the position of the optic nerve head relative to the fovea; the position of the temporal raphe; and axial length. While it is well established that axial length shows significant variance between individuals,[12] published data on the population variance of other key parameters is relatively recent. Chauhan and Burgoyne[13] provided a histogram of the distribution of ONH positions relative to the fovea in a population of 222 patients with ocular hypertension or glaucoma, and showed that the position of the centre of the ONH (centre of Bruch's membrane opening) relative to the fovea could differ by up to 25 degrees. A larger population distribution from the Beijing Eye Study showed a distribution from 6.3° to 28.9°.[14] The temporal raphe is now directly visible using high resolution OCT[15, 16] and adaptive optics.[17] The sample size of studies that have visualised and mapped the raphe are relatively small (approximately 20 people), however the angle of the temporal raphe appears to vary between individuals by up 10 degrees, with an on-average positioning of approximately 170 degrees from the ONH-fovea angle.[15, 16] Variation in the position of the temporal raphe has been confirmed by studies that have used lower resolution clinical OCT to look for divisions between superior and inferior hemifields in macular cube data.[18] The temporal raphe is a key

landmark dividing the superior and inferior retina and many analysis procedures for glaucoma (for example: the glaucoma hemifield test[19]) assume a horizontal boundary between the superior and inferior visual field. Hence, if the temporal raphe deviates significantly from horizontal, there is the potential for very atypical mapping between visual field locations in the nasal visual field and the optic nerve, and possibly misinterpretation of clinical analytics that assume a strictly horizontal divide between the superior and inferior hemifields.

The observation of significant population variance in these key anatomical features predicts that custom, personalised, mapping between structure and function might have clinical utility.[4, 9, 15] For example, personalised mapping may be important to detect early, spatially localised, signs of progression (for example, mapping pointwise visual field change to sectoral change of neuroretinal rim tissue or retinal nerve fiber layer); or to enable customised functional testing that is spatially directed by structural abnormalities observed on OCT.[20] To date, while customised mapping has been proposed,[2, 4] there has been fairly limited exploration of when and for whom, it is likely to be useful. Danthurebandara et al[21] compared the strength of correlations between structure and function for individually customised mapping[4] to a commonly used population based map[3] and found that performance of the two mapping schema was similar. Hood et al[11] considered individual differences in the position of the ONH relative to the fovea, and similarly found that on average, between group estimates of the strength of correlation between structure and function were not improved. These outcomes are hardly surprising given that most individuals within a population will have fairly average anatomy and therefore the customised approach and non-customised approach will produce very similar maps for many people. Consequently, when data across the population is pooled for analysis, and most people are "average", an absence of an "on-average" difference between customised and non-customised mapping schema is entirely predictable. A pertinent challenge arising is to identify the situations where customised mapping departs significantly from the population norm and how commonly this occurs.

In this paper, we approach this problem by calculating the likelihood of an individual having a structure-function map that significantly deviates from average, and illustrate the key anatomical

121 factors that result in such a situation. The purpose of our analysis was to determine who might benefit
122 from customised structure-function mapping in a clinical setting.

123

124 Methods

125 We have previously developed and described a computational model that outputs a customised map
126 from sectors on the ONH to locations in the visual field given input biometric parameters (distance of
127 the ONH centre from the fovea in horizontal and vertical directions, axial length, position of the
128 temporal raphe).[4, 5, 22] Our model provides mapping from any location (in x,y coordinates) in the
129 visual field to a resolution of 1 degree of angle on the ONH. For the purposes of the analysis
130 described herein, we restrict our mapping to the visual field locations included in the 24-2 pattern
131 (Humphrey Field Analyzer, Carl Zeiss Meditec, Dublin CA, USA).

132 Some graphical examples of the maps produced by our model are shown in Figure 1. In this example,
133 the horizontal displacement of the ONH relative to the fovea is kept fixed, while the vertical
134 displacement varies. The temporal raphe is fixed at 170 degrees from the angle between the fovea and
135 the optic disc (FoDi) angle because the limited data available from high resolution imaging of the
136 temporal raphe is consistent with this average value.[15, 16] The effect of changing axial length is also
137 illustrated.

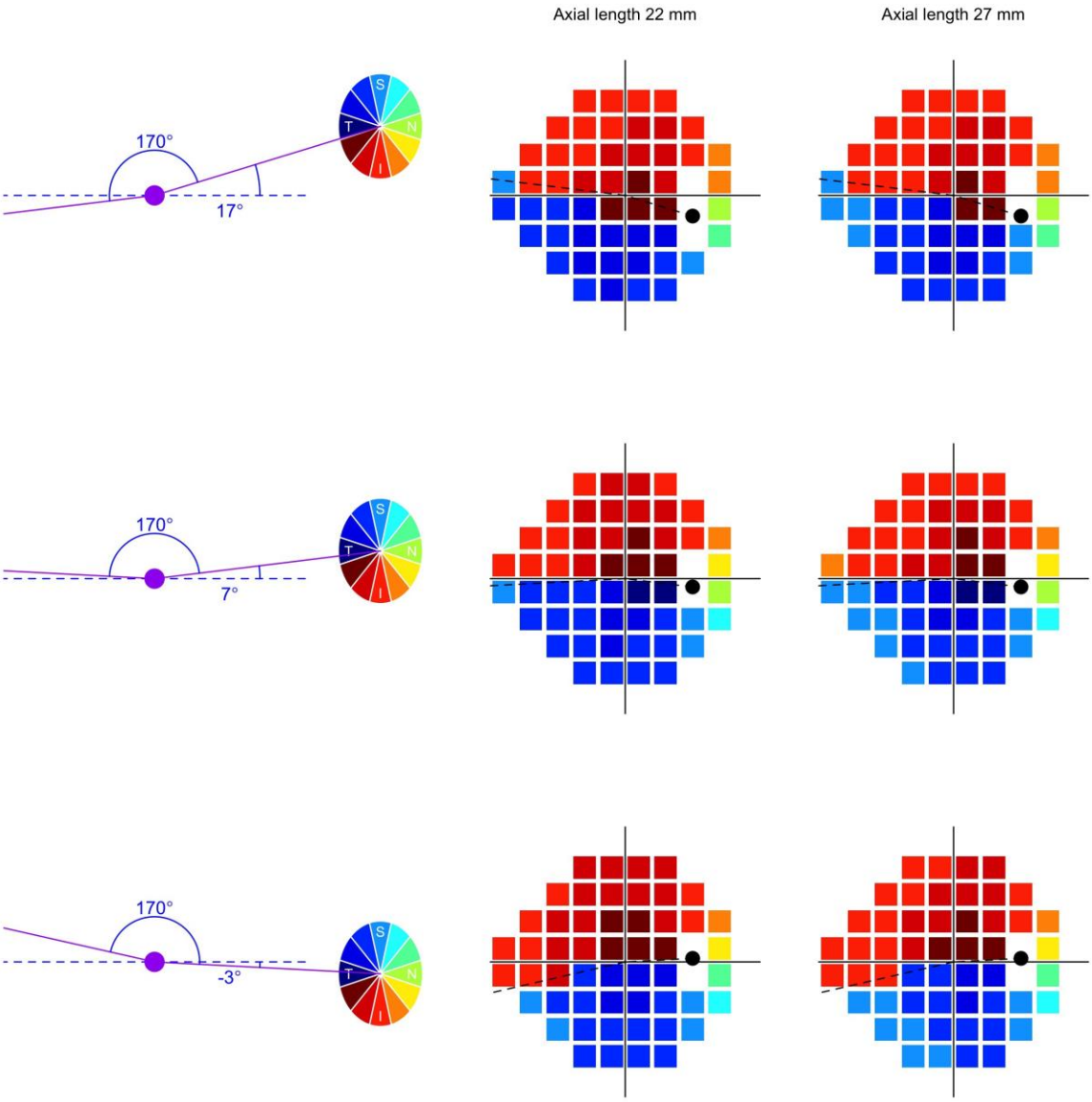


Figure 1: *Schematic illustration of customised mapping from 30 degree sectors of the optic nerve head to the 24-2 locations in visual field space in right eye format. The left hand side shows three different positions of the optic nerve relative to the fovea. Corresponding maps for both shorter and longer axial lengths are illustrated on the right hand side.*

Including all plausible anatomical variants of the parameters that input into the model results in over 11550 maps.[4] However some of these are much more frequent than others. In order to explore the expected frequency of "atypical" mapping, we used data from 2836 eyes from the Beijing Eye Study. The Beijing Eye Study 2011 was a population-based cross-sectional survey performed in an urban

region and a rural region of Beijing in Northern China and included adults with an age of over 50 years. It has been described in detail previously. [14, 23, 24] The Beijing Eye Study received human research ethics approval from the Medical Ethics Committee of the Beijing Tongren Hospital and all participants gave informed written consent. For this study we used the following information from each eye: axial length, distance of the centre of the optic nerve head from the fovea in both horizontal and vertical dimensions as derived from retinal photography using fundus camera Type CR6-45NM; Canon Inc., Tokyo, Japan (for further details of the procedure to derive the optic nerve position see:[14]) For all analyses we assumed that the position of the temporal raphe was 170 degrees from the angle between the fovea and disc (FoDi angle) as illustrated in Figure 1, as the position of the raphe was not individually measured in the Beijing Eye Study and previous studies suggest an angle of approximately 170 degrees on average.[15, 16] In order to project the ONH position onto a blind spot position on the visual field, we assumed a nodal point that was 17.2 mm for an eye with axial length 22.2mm,[25] and scaled it directly with axial length. The data included significant population variance in axial length and in the angle of the ONH from the fovea (Figure 2), as well as the distance from the fovea in x, y coordinates.

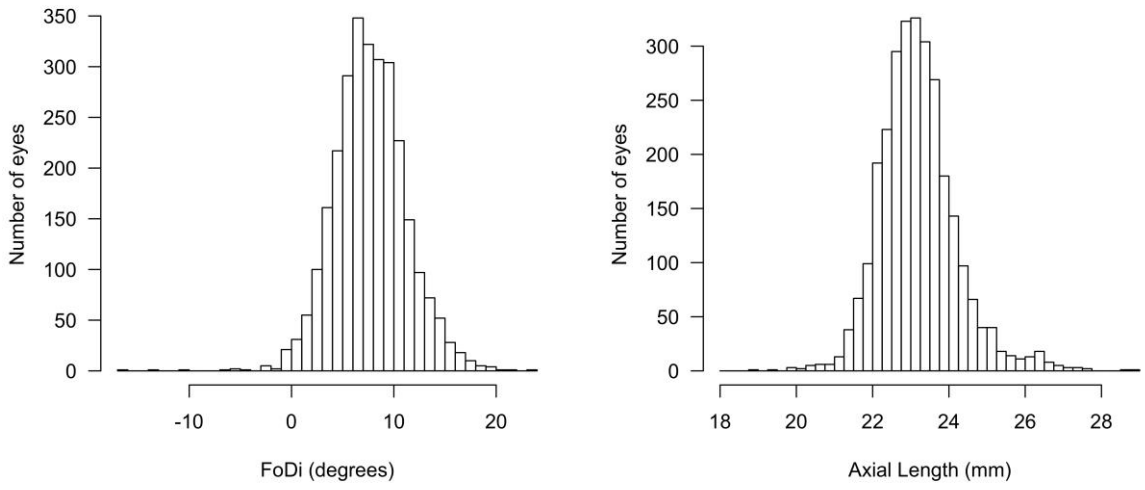


Figure 2: *A) Distribution of axial lengths within the population database; B) Distribution of angles between the fovea and the optic disc (FoDi) within the population. The sign of the FoDi angle is as per the schematic illustration in Figure 1.*

Analysis

Our baseline condition is the map for the "average eye" within the Beijing Eye study dataset (axial length 23.23mm, FoDi angle 7.672 degrees, distance from fovea to ONH centre 4.68mm), as illustrated in Figure 3. To determine the "average eye" in the data set we first computed the mean of each of three parameters: axial length (23.19mm), fovea-disc angle (7.68 degrees), and fovea-disc distance (4.77mm) the hypotenuse of fovea-disc in the horizontal and vertical dimensions) over the whole data set. To ensure that we had an anatomically plausible combination of the three parameters, we then selected the eye in the data set that had the smallest sum-of-squared distance from these three mean values to be the average. The average map in Figure 3 is similar to other published mapping schema that have been derived as the "best fit" from a population of eyes.[1, 3]

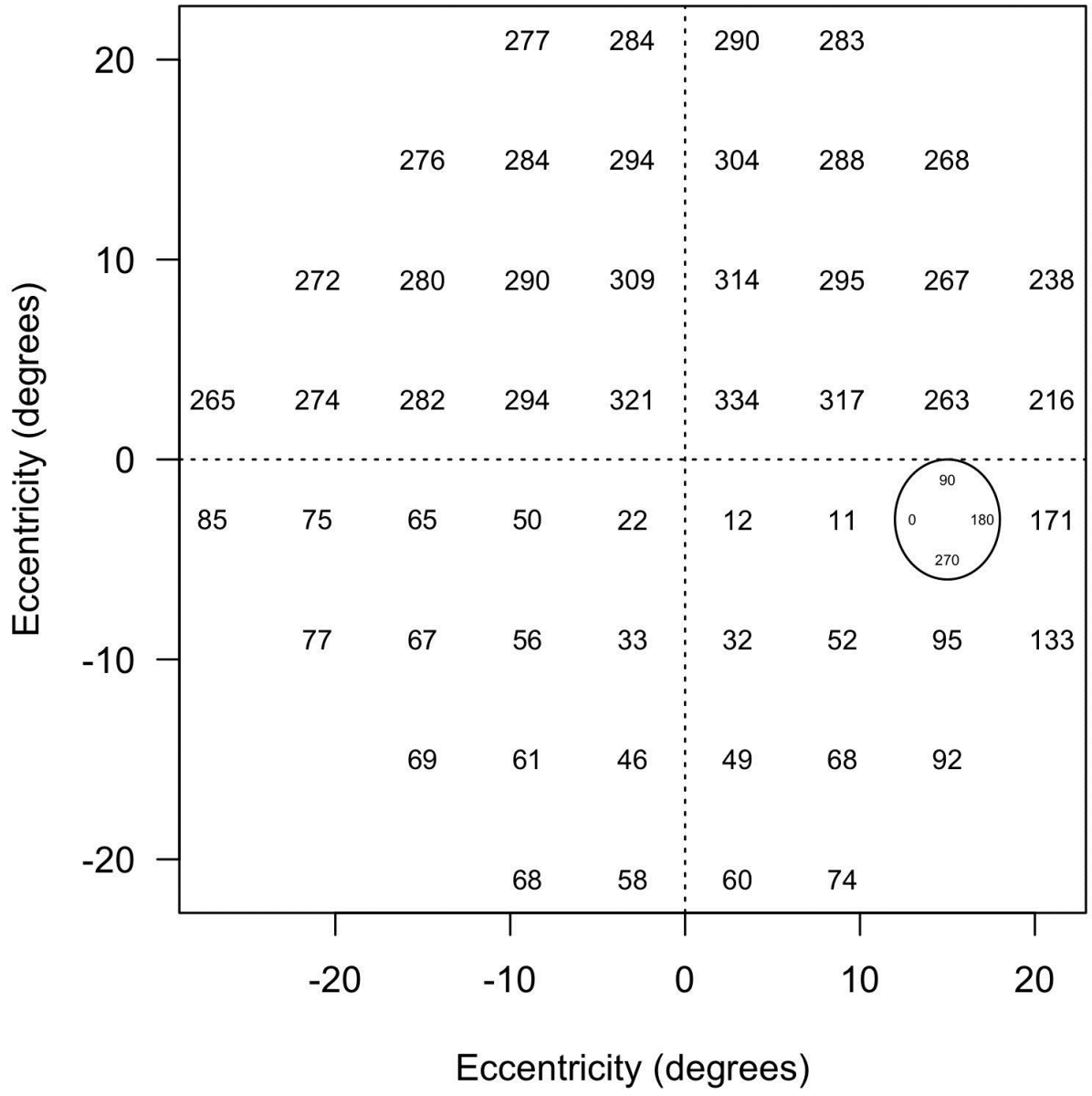


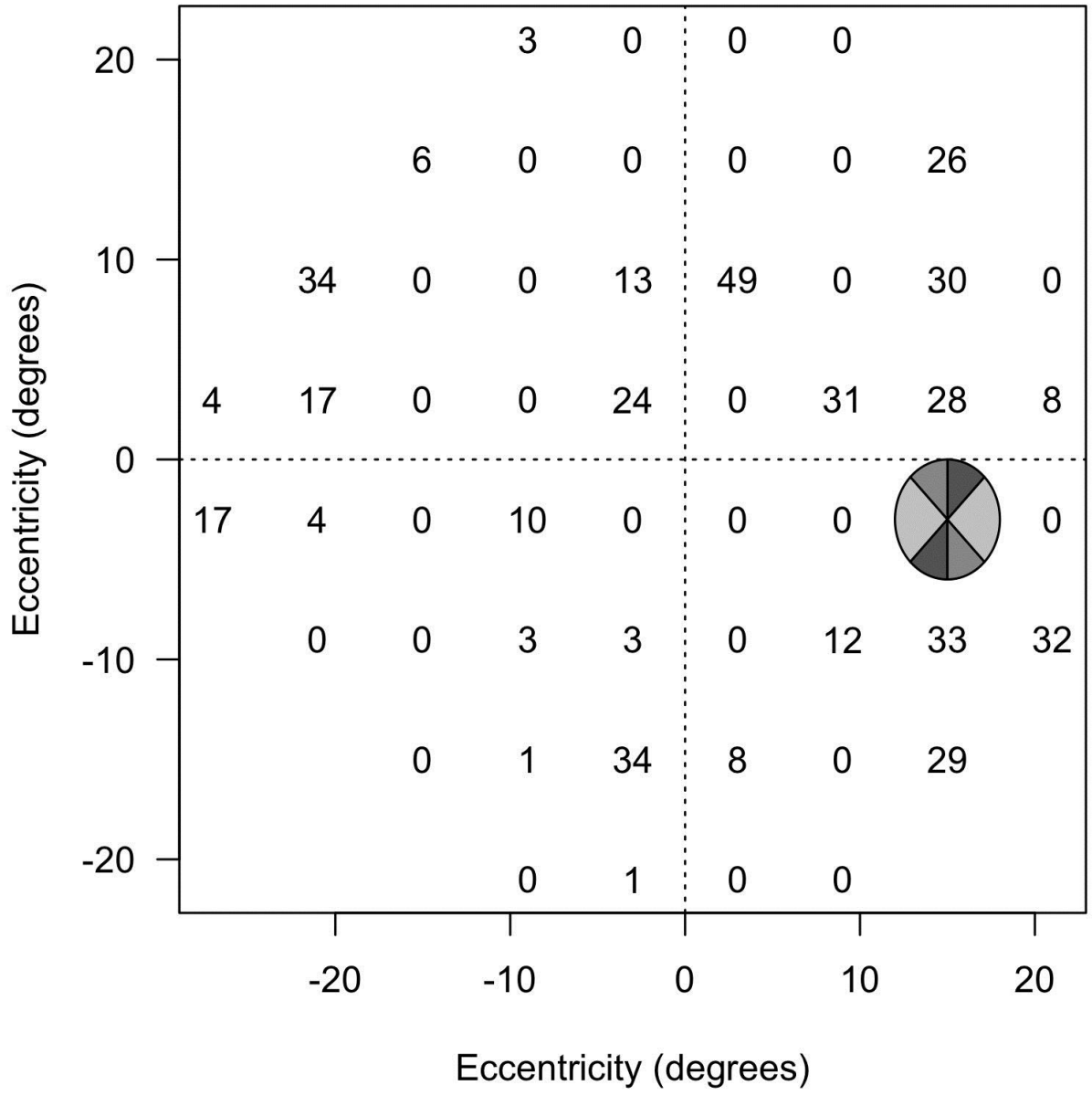
Figure 3: *The structure to function map for the average eye. Each location in visual field space from the 24-2 test pattern is represented. The number at each test location is the estimated angle of insertion (in degrees) of the retinal nerve fibers into the ONH that correspond to the specific location in visual space.*

In order to quantify the difference between using an individualised map versus the average-eye map, we report the following two items for each location in the 24-2 test pattern.

1) The proportion of eyes where at least one visual field location moved to a different sector within a predefined division of the ONH into 6 large sectors. Large sector maps are in common usage in current clinical instrumentation, principally derived from the mapping schema reported by Garway-Heath et al[26].
2) The proportion of eyes where the mapped point on the ONH was more than 15 degrees, 30 degrees or 60 degrees away from the insertion point for the same location in the eye with the population average anatomy.

Results

Figure 4 shows the percentage of eyes where each individual 24-2 visual field location mapped to a different ONH sector than described for the average eye using the six large ONH sectors in common clinical use.



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199 **Figure 4:** *For each 24-2 visual field location, the percentage of eyes in the population database that*
200 *fall into a different ONH sector than that of the average eye. The ONH is divided into the 6 sectors of*
201 *the Garway-Heath map[26] (as illustrated) at the blind spot in the visual field at (-15, -2) for a right eye.*

202

203 Figure 5 shows the percentage of eyes that deviated from the average-eye map by more than 15
204 degrees, 30 degrees or 60 degrees, for each location in the visual field. For the more than 60 degree
205 case, in all eyes, the locations mapped to the opposite pole of the ONH than conventionally

considered (as per Figure 1 upper and lower panel). A total of 12% of individuals showed this pattern of results.

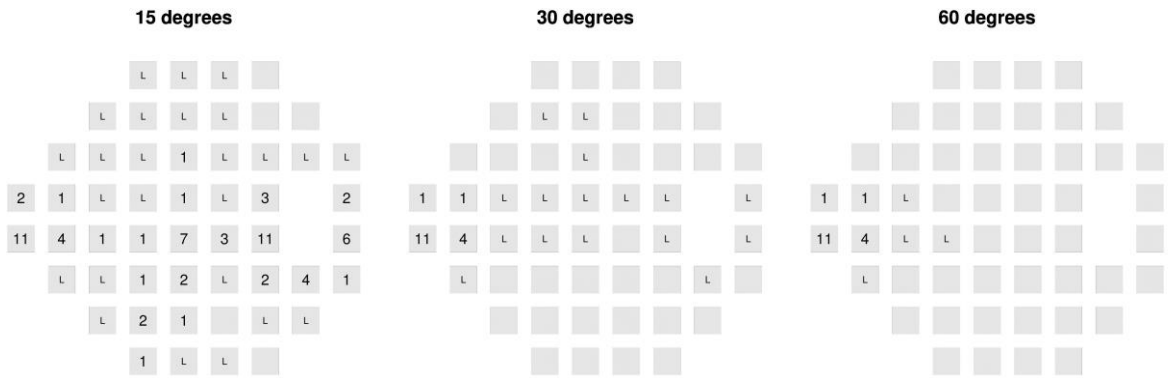
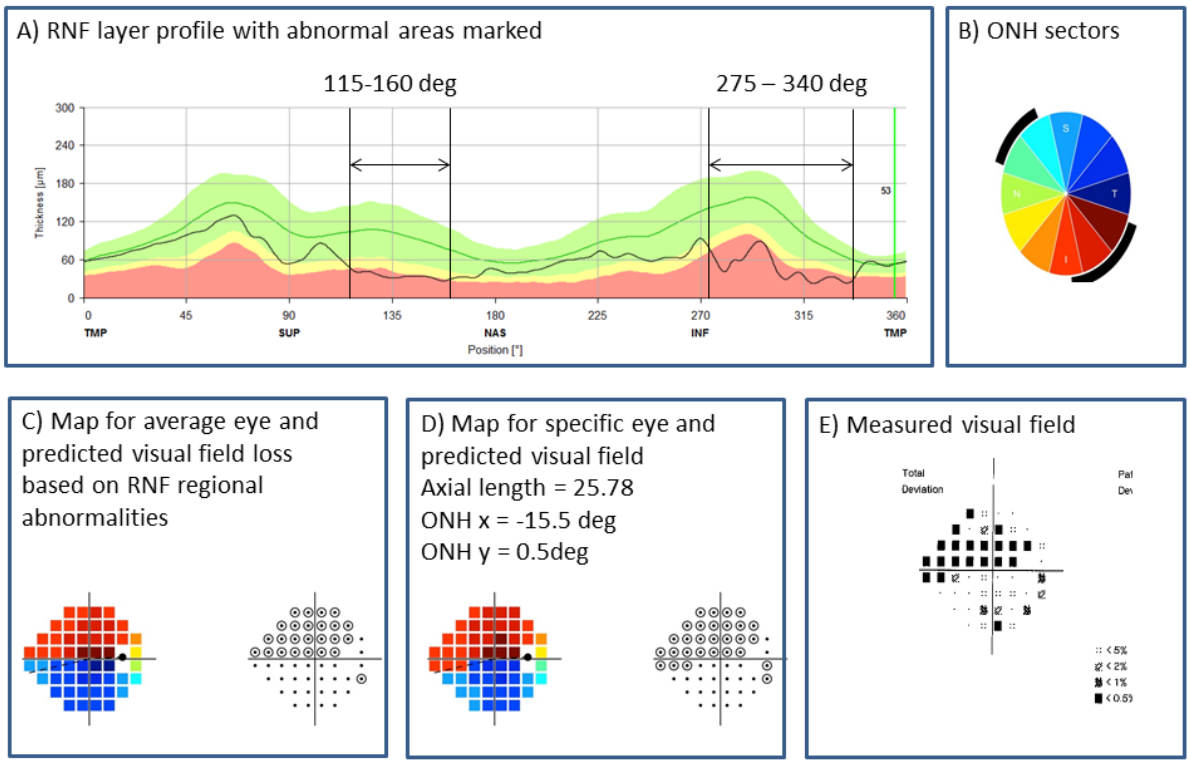


Figure 5*: For each location in the visual field, the percentage of eyes where the mapped location for the individualised structure-function map deviated from the average-eye map by more than 15 degrees (left panel), 30 degrees (middle panel) and 60 degrees (right panel). The proportion is represented numerically, with locations where the proportion was larger than 0 but less than 0.5% marked with an L.*

Comparison of Figure 5 to Figure 4 illustrates that many of the eyes that mapped into a different large sector from the average eye (Figure 4) were actually displaced by less than 15 degrees (Figure 5). Shifts of between 15-30 degrees were present largely for visual field locations along the nasal horizontal midline and are mainly driven by variation in the position of the optic nerve head relative to the fovea. Large deviations (greater than 60 degrees) from the average eye were noted in the nasal step region, in particular inferiorly. These arise from non-horizontal positioning of the temporal raphe, which results in the visual field location mapping to the opposite vertical pole of the optic nerve than traditionally assumed by a strictly horizontal raphe (Figure 1).



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224 ***Figure 6****: A primary open angle glaucoma patient case example (right eye) that illustrates departure*
225 *from average-eye structure-function mapping. A) a peripapillary RNFL OCT scan with two areas of*
226 *abnormal RNFL thinning marked; B) colour code for the division of the ONH into 12 x 30 degree*
227 *sectors; C) coloured map for the average eye where the colours for each visual field location indicate*
228 *the relevant sector on the ONH in panel B, and the grey scale visual field map marks the expected*
229 *locations of visual field damage from the damaged RNFL sectors marked in panel A; D) as per panel*
230 *C but for a map customised to the axial length and ONH position of the individual; E) the measured*
231 *24-2 visual field damage.*

232

233 Figure 6 shows a clinical example of the type of scenario where the mapping is significantly deviated
234 from average in the nasal step region. Figure 6A shows the OCT RNFL peripapillary scan
235 (Spectralis, Heidelberg Engineering GmBH, Heidelberg, Germany) for an individual with primary
236 open angle glaucoma. The RNFL profile shows two sectors of abnormality: between approximately

115-160 degrees, and between approximately 275-340 degrees. Panel 6B marks those regions on the ONH sectorial depiction. Panel 6C shows the predicted locations of visual field damage based on the average-eye map. However, this eye is not average and instead has an ONH minimally displaced from the horizontal midline (ONH x = -15.5 deg, ONH y = 0.5deg, fovea to disc angle = -3.1deg; axial length = 25.78mm). Panel 6D shows the predicted locations of visual field damage based on the individual eye's geometric parameters. Panel 6E shows the actual measured visual field for this individual (Humphrey Field Analyser, 24-2 SITA standard).

Discussion

Significant anatomical variation exists between individuals for ocular parameters that influence the mapping between common clinical structural measures, and locations in visual space. Such variation is sufficient to result in different maps between locations in visual field space and the ONH. The largest displacement is in the nasal step region of the visual field (temporal retina). Our analysis of the population-based data from the Beijing Eye Study predicts that approximately 12% of people will have markedly altered mapping between structure and function for visual field locations in this area (mapping to the opposite side of the ONH than traditionally assumed – see Figure 5, and schematically in Figure 1). Other smaller areas of displacement also occur, but given the resolution of current clinical analysis of the ONH and the expected pattern of loss in glaucoma, arguably the most clinically significant area of errors in mapping arise for the nasal step region of the visual field.

While our model can map to 1 degree resolution on the ONH, we have previously shown that measurement error in the various parameters relevant to customised mapping (position of the ONH, axial length) produces a practical sector limit of approximately 30 degrees for clinical use.[9] Most current clinical mapping schema include wider sector boundaries than 30 degrees. Improved precision of customised mapping should enable more anatomically localised linking of data from structure to

function. It remains to be seen whether more localised mapping results in better ability to monitor combined change in structural and functional parameters in glaucoma, however, it is likely that when smaller ONH sectors are used to enhance the spatial resolution of mapping the importance of personalising the maps will increase as fewer patients will fit within the "average" template since small deviations from average will be more likely to result in changes in mapped ONH sector (Figure 5). Similar to our current study however, the importance of personalising structure-function mapping in monitoring spatially localised progression will be best assessed through analysis of individual eyes with non-average anatomical parameters, rather than by comparison of population metrics.

Advances in OCT technology have resulted in ocular imaging being used very routinely in glaucoma management. The anatomical parameters that are required for custom mapping are macro-features (in particular, the position of the ONH relative to the fovea) so do not necessary require OCT to acquire, but are now exported routinely with several commercial OCT systems. Hence, incorporating a more customised approach to structure-function mapping should be relatively simple. An exception is the determination on an individual basis of the positioning of the temporal raphe, which currently requires custom high resolution imaging to accurately measure. For this reason, the absence of individual data regarding the positioning of the temporal raphe is a limitation of this study. We make the simplifying assumption that the temporal raphe is typically positioned at an angle of 170 degrees from the fovea-disc angle (see Figure 1). Available evidence suggests that this assumption is reasonable "on-average", however, given that we are specifically interested in the non-average eye, there will be cases where this relationship does not hold. Indeed, inspection of the data from the 15 eyes presented in Chauhan et al,[15] suggests some significant variation around the approximate average of 170 degrees from the fovea-disc angle. With only 15 eyes, however, it is not possible to derive a predictive relationship between the parameters that were measured in the Beijing data, and the position of the raphe (if, indeed, there is such a relationship). Clearly, further refinement of the predictions made by our analysis will be possible if a large database with all of axial length, fovea-disc angle and individually measured temporal raphe is available in the future.

We estimated the temporal raphe at 170 degrees from the fovea-disc angle based on previous literature,[15] and it is clear that in a significant proportion of eyes, the temporal raphe is not strictly horizontal. Here, we only present mapping data for the 24-2 visual field pattern (6 degree spacing, across the central +/- 24 degrees of visual field). Non-horizontal positioning of the temporal raphe is also predicted to significantly alter the mapping for the 10-2 visual field pattern, which covers a smaller visual eccentricity, but presents data closer to the horizontal midline, in addition to other commonly used patterns that place points close to the horizontal midline (eg the G-pattern in the Octopus perimeter). The model used to customise mapping between visual field locations and sectors on the optic nerve head within this study uses a few simple input parameters (axial length, x-y distance of the fovea from the optic nerve head, position of the temporal raphe), as these are considered major, macro-anatomical features that are likely to significantly alter the anatomical trajectories for retinal nerve fibre bundles from the retinal periphery to their point of insertion on the ONH. Other retinal features may be important for structure-function mapping, such as the position of the major retinal blood vessels,[27] or individual differences in retinal ganglion cell numbers and density across the retina, or individual differences in the shape of the macular region.[10, 28] Such features were not included in this study. Future work may refine the features that contribute to localised differences in structure to function mapping, however, we expect that major, clinically significant, differences between individuals (for example, complete swapping in mapping from inferior to superior hemifields) will be primarily driven by macro features such as the positioning of the raphe, and hence are encapsulated herein.

In this study, we chose to use the average eye from within our database as the comparison for analysis rather than an established structure-function map. Our average map is similar to the map of Garway-Heath[26] with one exception. The visual field locations superior nasal and inferior nasal to the blind spot take a more linear path in our model than the Garway-Heath population average map. It is worth noting that the map of Garway-Heath was derived from averages across the population for each location in the 24-2 visual field space, hence it is possible that no eyes within the dataset used to construct the map actually conformed to the derived average map for all visual field locations.

Furthermore, the Garway-Heath map was derived from a substantially different ethnic demographic than the population of eyes included here (69 eyes from the United Kingdom versus 2836 eyes from China). Consequently, we decided that comparison to our average modelled eye was a fair exploration of the effects of varying local anatomical parameters and likely to lead to more conservative estimates than comparing to a schema derived in a different population.

Individualised mapping between structure and function could potentially be utilised clinically in several ways. For example, localised structural damage could be used to seed visual field test algorithms[29, 30] or could prompt the targeting of specific localised areas of the visual field for denser sampling or resampling to ensure that more reliable estimates of performance are obtained in key areas of clinical interest. Alternately, new analysis methods that combine probabilities of progression from visual field and imaging data[31] could be applied on a localised scale. For the average-eye, reasonable assumptions could be made for such analysis from a population average mapping schema, however, our analysis here shows that for a small proportion of eyes an individualised approach is necessary to avoid gross mistakes in mapping.

Conclusions

Population variance in the position of the optic nerve head , axial length and the location of the temporal raphe, predict that individual mapping between visual field locations and sectors on the optic nerve head may be clinically useful. We show that anatomically customised mapping shifts the map markedly in approximately 12% of the general population in the nasal step region where visual field locations can map to the opposite pole of the optic nerve head than traditionally considered.

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