AMERICAN ACADEMY OF OPHTHALMOLOGY
The Eye M.D. Association

# Enhancing Structure–Function Correlations in Glaucoma with Customized Spatial Mapping

*Shonraj Ballae Ganeshrao, MPhil,*[1,2] *Andrew Turpin, PhD,*[1] *Jonathan Denniss, PhD,*[1,2,3] *Allison M. McKendrick, PhD*[2]

***Purpose:*** To determine whether the structure–function relationship in glaucoma can be strengthened by using more precise structural and functional measurements combined with individualized structure–function maps and custom sector selection on the optic nerve head (ONH).

***Design:*** Cross-sectional study.

***Participants:*** One eye of each of 23 participants with glaucoma.

***Methods:*** Participants were tested twice. Visual fields were collected on a high-resolution 3° × 3° grid (164 locations) using a Zippy Estimation by Sequential Testing test procedure with uniform prior probability to improve the accuracy and precision of scotoma characterization relative to standard methods. Retinal nerve fiber layer (RNFL) thickness was measured using spectral-domain optical coherence tomography (OCT; 4 scans, 2 per visit) with manual removal of blood vessels. Individualized maps, based on biometric data, were used. To customize the areas of the ONH and visual field to correlate, we chose a 30° sector centered on the largest defect shown by OCT and chose visual field locations using the individualized maps. Baseline structure–function correlations were calculated between 24-2 locations (n = 52) of the first tested visual field and RNFL thickness from 1 OCT scan, using the sectors of the Garway-Heath map. We added additional data (averaged visual field and OCT, additional 106 visual field locations and OCT without blood vessels, individualized map, and customized sector) and recomputed the correlations.

***Main Outcome Measures:*** Spearman correlation between structure and function.

***Results:*** The highest baseline correlation was 0.52 (95% confidence interval [CI], 0.13–0.78) in the superior temporal ONH sector. Improved measurements increased the correlation marginally to 0.58 (95% CI, 0.21–0.81). Applying the individualized map to the large, predefined ONH sectors did not improve the correlation; however, using the individualized map with the single 30° ONH sector resulted in a large increase in correlation to 0.77 (95% CI, 0.47–0.92).

***Conclusions:*** Using more precise visual field and OCT measurements did not improve structure–function correlation in our cohort, but customizing the ONH sector and its associated visual field points substantially improved correlation. We suggest using customized ONH sectors mapped to individually relevant visual field locations to unmask localized structural and functional loss. *Ophthalmology 2015;■:1–11 © 2015 by the American Academy of Ophthalmology.*

Most studies of the relationship between structure and function in glaucoma using cross-sectional clinical data have revealed a relatively weak relationship.[1–7] Structural measures poorly predict function and vice versa, with many reasons for this finding suggested. These include imprecision and inaccuracy of the structural and functional measures; the suitability of comparing across different measurement scales; individual differences in the number of retinal ganglion cells before disease; and anatomic differences between people resulting in different spatial mapping between structural and functional measures (for detailed reviews see Anderson,[8] Malik et al,[9] and Harwerth et al[10]). In this study, we attempted to reduce variability resulting from 2 of these factors by reducing measurement error in both structural and functional measurements and by using a spatial map altered to account for individual anatomic differences.

Visual field measurements show considerable variability in damaged locations,[11] and clinical visual fields usually are estimated by sparsely sampling the central 24° of vision, typically at approximately 54 locations. Current visual field test strategies have inherent measurement bias that can be minimized by altering the thresholding algorithms[12] to allow more accurate and precise estimates of damage. Furthermore, a denser grid of test locations can enable the detection of visual field defects not revealed by the standard 24-2 grid.[13–15] Similarly, the accuracy of estimates of retinal nerve fiber layer (RNFL) thickness measured using optical coherence tomography (OCT) is affected by various factors, including media



http://dx.doi.org/10.1016/j.ophtha.2015.04.021
ISSN 0161-6420/15

opacity, pupil diameter, sample density, type of scan, signal strength, low RNFL thickness, OCT segmentation, algorithm errors, and eye movements.[16–19] In addition to these factors, locations of major blood vessels correlate well with the peaks of RNFL thickness, indicating that part of the thickness profile measured by OCT includes blood vessels, a component that also varies between individuals.[20]

To correlate localized structural defects with functional performance, a spatial map connecting the 2 is required. There are various maps in the literature,[3,21–27] with arguably the most commonly used for structure–function studies being the Garway-Heath (G-H) map.[21] A limitation of the G-H map as typically applied is that it describes the population average mapping between locations in the visual field to fairly large sectors on the optic nerve head (ONH). Recent studies have shown that the spatial map varies significantly because of individual differences in ONH position, ONH dimensions, and the axial length.[28,29] Furthermore, Garway-Heath et al[21] recommend dividing the ONH into 6 fixed sectors (four 40° sectors, one 90° sector, and one 110° sector) as a compromise between minimum practical sector size and the number of visual field points in each sector. There are several potential problems with using 6 fixed sectors: (1) small RNFL defects can be lost because of averaging across large sectors, and (2) if a localized RNFL defect lies across the boundary of 2 sectors, then often neither of the sectors reflect the defect. Therefore, we propose that using smaller, customized sectors will improve the ability to unmask localized RNFL defects.

To address the limitations described above, we improved structural and functional measures and used individualized structure–function mapping. Specifically, we (1) measured visual fields twice using a higher spatial resolution grid than the 24-2 grid and using an algorithm that improves accuracy and precision relative to Swedish Interactive Threshold Algorithm (SITA)–like test procedures[12]; (2) measured RNFL thickness at 2 separate visits using spectral-domain OCT, which has better reproducibility than time-domain OCT,[19,30,31] and removed the blood vessel component from the RNFL thickness profiles[32]; (3) used individualized spatial structure–function maps that take into account individual anatomic differences[26]; and (4) chose customized 30° ONH sectors to explore the most abnormal areas for an individual.

We aimed to determine whether structure–function correlation can be increased by improving structural and functional measurements and by using an individualized structure–function map. We also were interested in whether the use of a customized map that allows the specific choice of a region of damaged RNFL results in a stronger link between structure and function.

## Methods

Glaucoma participants were recruited from our previous research participant database and by an advertisement placed in the Glaucoma Australia newsletter. All had a confirmed ophthalmologic diagnosis of open-angle glaucoma and were being treated. Ethical approval for the study was obtained from the University of Melbourne Human Research Ethics Committee. All participants signed an informed consent form in accordance with the tenets of the Declaration of Helsinki.

Each participant underwent a comprehensive eye examination including visual field examination, OCT (Spectralis; Heidelberg Engineering GmbH, Heidelberg, Germany), and Heidelberg Retinal Tomography (Heidelberg Engineering GmbH). All participants had a glaucoma probability score flagged as abnormal in at least 1 sector on their Heidelberg Retinal Tomography results. Participants with visual acuity less than 6/9, refractive error outside the range of ±6 diopters (spherical equivalent), tilted optic disc or any other optic disc abnormalities, any ocular disease other than glaucoma, or diabetes were excluded. In addition to these, people with a history of migraines also were excluded because migraine is associated with visual field defects.[33–35] The eye that satisfied our inclusion criteria was tested; if both eyes were eligible, then 1 eye was chosen at random.

### Visual Fields

Visual fields were measured twice using an intensive custom strategy implemented on an Octopus 900 perimeter (Haag-Streit AG, Koeniz, Switzerland) via the Open Perimetry Interface.[36] The test used a 3°×3° grid (164 locations; Fig 1), which has higher spatial resolution than the 24-2, 6° × 6° grid, and an unbiased prior Zippy Estimation by Sequential Testing (ZEST) test strategy. Locations were within the same region as the common 24-2 pattern, except for 2 additional points at (27°, ±6°) from fixation to better test the nasal field. To estimate macular defects, 4 additional locations were tested at (±1°, ±1°) from fixation. A uniform probability mass function (PMF) that makes no initial assumption about the location's sensitivity was used as a prior. It has been shown that a uniform prior ZEST strategy reduced measurement bias and improved precision relative to the more commonly used SITA-like test strategies, at a cost of longer test duration.[12]

The ZEST test strategy used in this study is described in detail elsewhere.[37,38] Briefly, it presents the mean of the prior PMF, and a likelihood function that depends on the patient's response then is multiplied with the prior PMF to generate a new PMF. This new PMF then serves as the prior, and the mean of this PMF is presented. This process continues until a PMF standard deviation or number of presentation criteria is met. The likelihood function used in our study was similar to the one used by Turpin et al[12]: a piecewise linear likelihood function that asymptotes at 0.05 and 0.95, with the middle line covering an interval of 3 dB. The stopping criterion was a PMF standard deviation of 1.5 dB or less.

The background intensity of the perimeter was 10 cd/m$^2$, stimulus size was Goldmann size III (0.43°), and maximum stimulus intensity used was 4000 asb (0 dB). Each stimulus was shown for 200 ms, with a subsequent response window of 1750 ms. If no response was noted within this window, then the response was considered not seen. After this response window, the perimeter waited briefly before presenting the next stimulus. The wait time was randomized between 300 and 500 ms for each trial. False-positive results were measured by presenting a stimulus outside the range of the instrument; if a response was noted within the response window for such trials, then it was recorded as a false-positive response. Throughout the test, fixation was monitored using the internal fixation monitor. False-negative rates were not measured because it was unclear how to do so accurately. It has been shown that higher rates of false-negative responses obtained in glaucoma subjects often are the result of