432 Structure-Function Relationships I
Wednesday, May 10, 2017 11:00 AM–12:45 PM
Ballroom 4  Paper Session
Program #/Board # Range: 4257–4263
Organizing Section: Glaucoma

Program Number: 4257
Presentation Time: 11:00 AM–11:15 AM
Structure-guided ANSWERS: detecting visual field progression with the assistance of spatially-related structural measurement
qian cheng,1 Haogang Zhu,1,2, David P. Crabb3, Paul H. Artes3, David Garway-Heath2.1 State Key Laboratory of Software Development Environment, Beihang University, Beijing, China; 2National Institute for Health Research Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology, London, United Kingdom; 3City University London, London, United Kingdom; 4Plymouth University, Plymouth, United Kingdom.

Purpose: ANSWERS (Zhu IOVS 2015) is a progression analysis method for the visual field (VF), which takes into account increasing VF variability during progression as well as spatial correlation amongst test locations. VF and imaging measurements of optic nerve (ON) structure are correlated. We evaluated the improvement in diagnostic precision by extending ANSWERS to incorporate spatially-related structural ON measurements.

Methods: Two sets of VF (Humphrey Field Analyzer, Carl Zeiss Meditec) and ON rim area (RA) (Heidelberg Retina Tomograph, Heidelberg Engineering) data were used. The ‘progression’ datasets were from The United Kingdom Glaucoma Treatment Study (UKGTS) comprising 659 eyes from 437 patients. The ‘stable’ dataset comprised 30 eyes from 30 glaucoma patients each of whom were retested 12 times within 2 months. Within a hierarchical Bayesian model in ANSWERS, the prior distribution of the VF progression rate at each VF location was set by the slopes and variance of the rate of change in the corresponding sectorial RA, leading to the structure-guided ANSWERS (sANSWERS). The progression indices from sANSWERS, ANSWERS and permutation of pointwise linear regression (PoPLR) were compared. Positive rate (as a surrogate for sensitivity) and false positive (FP) rate were quantified on the ‘progression’ and ‘stable’ datasets, respectively, at various series lengths. Survival analysis was also performed to test the ability to distinguish the treatment and placebo arms in the UKGTS dataset.

Results: In all series lengths, the positive rate of sANSWERS was higher than those of ANSWERS and PoPLR at equivalent FP rates (Figure). The improvement was greatest in short subseries. Specifically, at 7th months, the positive rate ratio at the 5% FP rate of sANSWERS over ANSWERS and PoPLR was 2.56 and 5.13, respectively. The survival analysis detected the difference between the treatment and placebo arms earlier than ANSWERS and PoPLR (Figure). sANSWERS needs 5 measurements (10 months) to detect significant difference while ANSWERS needs 7 (16 months) at a 5% FP rate.

Conclusions: With the extra information from spatially-related structural measurements, sANSWERS is more efficient at detecting VF progression and can capture the treatment effect earlier than ANSWERS and PoPLR in a clinical trial.

Commercial Relationships: None

Program Number: 4258
Presentation Time: 11:15 AM–11:30 AM
The Macula Progression Study (MAPS): Repeatability of a Single, Wide-field, Swept-Source Optical Coherence Tomography Protocol
C Gustavo De Moraes, Jeffrey M. Liebmann, Jeremy Reimann, Lam Lu, Lama Al-Aswad, Dana Blumberg, George A. Cioffi, Robert Ritch, Donald Hood. Ophthalmology, Columbia University Medical Center, New York, NY.

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Purpose: Commercially-available software for detecting progression with OCT do not employ a reference database with patient data repeated over short intervals to help differentiate progression from variability. We have described and validated a single wide-field swept-scan optical coherence tomography (ssOCT) protocol to diagnose early glaucoma.[1] To test the feasibility of using this single scan protocol to detect the progression of glaucoma, we assessed the repeatability of its measures.

Methods: In this prospective cohort study, we included 124 eyes (124 subjects) (52 healthy controls; 16 glaucoma suspects; and 56 early manifest glaucoma) with 24-2 mean deviation (MD) > -6 dB). All participants had ssOCT wide-field scans (9x12 mm, DRI-OCT, Topcon, Inc., Tokyo, Japan) and 24-2 and 10-2 visual field tests on the same day, which were repeated at least four times within an 8 week period. For quantitative analysis, we calculated the 90% limits of variability of local and global macular retinal ganglion cell plus inner plexiform layer (RGC+) and circumpapillary retinal nerve fiber layer (cpRNFL) thicknesses. Changes exceeding the upper 5% and 1% limits are deemed “possible” and “likely” progression, respectively. For qualitative analysis, two expert graders reviewed all sequential images to assess the repeatability of the single wide-field ssOCT report.

Results: The repeatability of RGC+ and cpRNFL thickness measurements was excellent (ICC= 0.96 and 0.98, respectively). The expert grader did not flag any significant changes in participants’ reports over time using the repeatability data. Figure 1 depicts an example of a patient with double arcuate scotomata affecting the macula. The wide-field reports of tests performed 4 weeks apart were very similar.

Conclusions: Given its excellent repeatability, a single wide-field ssOCT report may be useful not only to diagnose early glaucoma, [1] but also to detect early signs of structural progression.

REFERENCE
1. Hood et al., TVST 2016;5(6):4

Commercial Relationships: C Gustavo De Moraes, None; Jeffrey M. Liebmann, Allergan Inc. (C), Alcon Laboratories Inc. (C), Dypsis Inc. (C), Carl Zeiss Meditec Inc. (C), Topcon Medical Systems Inc. (C), Pfizer Inc. (C); Jeremy Reimann, None; Lam Lu, None; Lama Al-Aswad, None; Dana Blumberg, None; George A. Cioffi, None; Robert Ritch, Ocular Instruments (P), Dypsis Inc. (C), Diopsys Inc. (I), Topcon Medical Systems Inc (C), Pfizer Inc. (C), Sensimed, AG (C), iSonic Medical (C), Topcon Medical Systems Inc (I); Donald Hood, Topcon, Inc. (C)

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Presentation Time: 11:30 AM–11:45 AM

A basis for customizing perimetric locations at the macula in patients with glaucoma

Muhammed S. Alhuwimi, William H. Swanson, Victor E. Malinovsky, Brett J. King, School of Optometry, Indiana University Bloomington, Bloomington, IN.
Methods: We recently described a method to automatically determine the orientation of the temporal nerve fibre raphe from OCT, using the intensity data from vertically oriented macular cube scans. Here, we used this method to measure raphe orientation bilaterally in 49 healthy participants (aged 19-81 years) and 51 participants with open-angle glaucoma (aged 51-80 years). The outcome measures were the angles measured between the fovea, disc and temporal raphe.

Results: Fovea-disc-raphe angle did not differ between groups (p=0.28) and was 173.5 ± 3.2° (range=166–182°) in the healthy group, and 174.2 ± 3.4° (range=166–184°) in glaucoma. The fovea-disc-raphe angle was not correlated with age or axial length (p > 0.4), showed some symmetry between eyes in the glaucoma group (R² = 0.31, p < 0.01), and little symmetry in the healthy group (p > 0.05). The fovea-disc angle was correlated with fovea-raphe angle (R² = 0.27, p <0.01), but was not a good predictor for raphe orientation (average error = 6.8°, maximum error = 15.6°). When compared to an assumption of a strictly horizontal raphe, the average error was 3.2° (maximum error = 9.6°).

Conclusions: There is substantial natural variation in the orientation of the temporal nerve fibre raphe, which cannot be accurately predicted from age, axial length, relative geometry of the disc and fovea, or parameters from the contralateral eye. Raphe orientation should be measured directly for accurate mapping between visual field and anatomical data in glaucoma.

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Presentation Time: 12:00 PM–12:15 PM
Comparison of within-eye and between-individual variability in macular structure-function relationships
Kourosh Nouri-Mahdavi1, Nima Fatehi1, Navid Amini1, Fei Yu1, Esteban Morales1, Sharon Henry1, Abdelmonem Afifi2, Anne Coleman1, Joseph Caprioli1. 1Ophthalmology, Stein Eye Institute, Los Angeles, CA; 2Biostatistics, Fielding School of Public Health, Los Angeles, CA.

Purpose: Significant variability is observed when structure-function (SF) relationships are examined using cross-sectional data. However, respective contributions of within-eye vs. between-individual variability components are not well defined. We tested the hypothesis that within-eye variability in SF relationships between macular thickness and central visual field (VF) sensitivities are lower than between-individual variability.

Methods: Glaucoma patients with macular SD-OCT images (Spectralis’ Posterior Pole Algorithm) and central 10-2 VF on ≥3 visits were enrolled from a longitudinal study. 57 eyes (57 patients) in which macular and total deviation (TD) values varied through their entire range were selected. Macular images were segmented and ganglion cell/inner plexiform layer (GCIPL) thicknesses were exported as horizontal 8x8 arrays of 3° superpixels. VF locations were adjusted for ganglion cell displacement (Figure 1) and bivariate SF plots were drawn for GCIPL thickness in 24 central superpixels and corresponding TD values. Mixed-effects regression analyses were performed on data repeated over time where SF relationships were modeled with fixed effects (broken stick model or transformed variables) while within-eye and between-individual variability were estimated from the variance of residual errors and random intercepts.

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respectively, and their comparisons were expressed as intraclass correlation coefficients (ICC).

**Results:** Average (±SD) mean deviation of 10-2 VFs was –9.7 (±4.9) dB. A broken stick model best fit the data when TD values were expressed in dB whereas a linear fit modeled the data best with TD values in 1/L units. Regardless of model or change point chosen for the broken stick model (–8 dB based on Miraftabi et al. 2016 or –5.5 dB based on data), magnitude of within-eye variability was consistently larger than between-eye variability (\(\sigma_{BE}^2 =0.036\) vs. \(\sigma_{WE}^2 =0.068\) for the model with highest ICC using data at peak ganglion cell density or 5.4° eccentricity). ICCs ranged from 0.173 to 0.345.

**Conclusions:** Within-eye variability of macular/central field SF models were larger than between-individual variability. This finding seems to be at least partially related to measurement noise and the wide range of macular thickness before early functional loss can be detected. Eye-specific SF models may not reduce variability of models predicting functional from structural measurements.

**Program Number:** 4262  
**Presentation Time:** 12:15 PM–12:30 PM

**Relationship Between Optical Coherence Tomography Angiography Macular Vascular Density Measurements and Central Visual Field Damage**

Rafaela C. Penteado1, Linda M. Zangwill1, Fabio B. Daga1, Mark Christopher1, Adeleh Yarmohammadi1, Patricia Isabel C. Manalastas1, Tadamichi Akagi1, 2, Takuhei Shoji1, 3, Felipe Medeiros1, Robert N. Weinreb1, 1Hamilton Glaucoma Center, Shiley Eye Institute, Department of Ophthalmology, University of California, San Diego, San Diego, CA; 2Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan; 3Department of Ophthalmology, Saitama Medical University, Iruma, Japan.

**Purpose:** To evaluate the association between macular vascular density assessed by optical coherence tomography angiography (OCT-A) and central visual field results in normal, glaucoma suspects and glaucoma eyes.

**Methods:** Participants of the Diagnostic Innovations in Glaucoma Study (DIGS) who had OCT-A images of the macula (AngioVue; Optovue, Freemont, CA) and central visual field 10-2 test were selected for this cross-sectional study. Only macular (3.0 x 3.0 mm) OCT-A scans labelled as having good quality according to the University of California, San Diego Imaging Data Evaluation and Analysis (IDEA) Reading Center protocol were included. The associations between central visual field mean deviation (MD), and both superficial macular whole-image vessel density (wiVD) and perifoveal vessel density (pfVD) were assessed using linear regression. Analysis of Variance (ANOVA) was performed to evaluate the differences in wiVD and pfVD amongst the different diagnostic groups.

**Results:** A total of 235 eyes from 41 healthy participants, 44 glaucoma suspects, 94 mild glaucoma patients, and 56 moderate to severe glaucoma patients were included. Mean wiVD (52.52%, 49.52%, 49.17% and 45.30%, respectively) and mean pfVD (54.84%, 51.83%, 51.87% and 47.74%, respectively) were found to be significantly higher in healthy eyes compared to glaucoma suspects and glaucoma patients with mild and severe disease in these four diagnostic groups (ANOVA p<0.001, and post-hoc Tukey-Kramer Test). The association between SAP 10-2 MD and wiVD (R²=15.87%) and between SAP 10-2 MD and pfVD (R²=14.74%) were statistically significant (p<0.001 for both).

**Conclusions:** Macular vascular density assessed by OCT-A is lower in patients with moderate to severe glaucoma when compared to healthy eyes, glaucoma suspects or mild glaucoma. Whole-image vessel density and perifoveal vessel density are also correlated with central visual field (SAP 10-2) mean deviation results, and future studies with macular OCT-A should be done in order to evaluate disease progression.
Figure 1. Boxplot depicting the distribution of macular whole-image vessel density (wiVd, in blue) and perifoveal vessel density (pfVd, in red) for healthy eyes, glaucoma suspects, mild glaucoma patients, and moderate to severe glaucoma patients.

**Commercial Relationships:** Rafaela C. Penteado, None; Linda M. Zangwill, National Eye Institute (F), Heidelberg Engineering GmbH (F), Topcon Medical Systems Inc. (F), Carl Zeiss Meditec Inc. (F), Optovue Inc. (F); Fabio B. Daga, None; Mark Christopher, None; Adeleh Yarmohammadi, None; Patricia Isabel C. Manalastas, None; Tadamichi Akagi, Alcon (R), Senju (R), Santen (R), Pfizer (R), Kowa (R); Takuhei Shoji, Alcon (R), Senju (R), Santen (R), Pfizer (R), Kowa (R), Otsuka (R); Felipe Medeiros, Alcon (R), Reichert (R), Sensimed (F), Allergan (F), Carl Zeiss Meditec (F), Allergan (R), Bausch & Lomb (F), Carl Zeiss Meditec (C), Novartis (C), Heidelberg Engineering (F), Carl Zeiss Meditec (R), Reichert (F), Merck (F), Alcon (F), Topcon (F), National Eye institute (R), Allergan (C); Robert N. Weinreb, Heidelberg Engineering (F), Aerie Pharmaceutical (C), Foresight Vision V (C), Alcon (C), Carl Zeiss Meditec (F), Sensimed (C), Quark (F), Topcon (F), Optovue (F), Eyenovia (C), Bausch & Lomb (C), Genentech (F), Allergan (C), Unity (C)

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**Presentation Time:** 12:30 PM–12:45 PM

**Quantification and functional correlations of macular microvasculature in the ganglion cell-inner plexiform layer in primary open angle glaucoma using OCT Angiography**

*Ingy Madi1, Arman Zaman1, Amir H. Kashani1, Zhongdi Chu2, Ruikang K. Wang2, Grace M. Richter1, 1USC Roski Eye Institute, Keck School of Medicine of University of Southern California, Los Angeles, CA; 2University of Washington, Seattle, WA.

**Purpose:** To quantify the microvasculature changes in the macula in primary open angle glaucoma (POAG) patients as measured from optical coherence tomography angiography (OCTA) en face images of the ganglion cell-inner plexiform layer; and to determine the strength of correlation of perfusion with hemifield mean deviation values.

**Methods:** 6x6 mm² scans of the macula were obtained on POAG and normal patients using the Angioplex spectral-domain OCTA, and Humphrey Visual Field 24-2 mean deviation (MD) defects were calculated for superior and inferior hemifields in each eye using proprietary formulas (Carl Zeiss Meditech; Dublin, CA). Prototype software was used: (1) to perform semi-automatic segmentation of the raw OCTA data to obtain a precise ganglion cell-inner plexiform layer (GC-IPL) en face image, and (2) to calculate perfusion parameters including vessel area density (VAD), vessel skeleton density (VSD), and vessel complexity index (VCI) for the macula (globally, hemifields, and other focal sectors) (Figure 1). Perfusion parameters in normal and glaucomatous eyes were compared using Wilcoxon rank sum test. Strength of correlation between each perfusion parameter and the corresponding hemifield MD values were calculated using Spearman’s rank correlation.

**Results:** The study included 20 POAG eyes (12 mild/moderate [5 of which were preperimetric] and 8 severe) and 16 normal eyes. 6 eyes showed no visual field defects, 7 eyes had superior VF defects only, 2 eyes had inferior VF defects only, and 5 eyes had both. VAD, VSD, and VCI were significantly reduced with worsening severity of glaucoma (VAD P=0.0047; VCI P=0.0016; P= VSD 0.0023 using Kruskal-Wallis test). Glaucomatous eyes had significantly reduced perfusion parameters compared to normal eyes. There was a strong correlation between inferior HVF mean deviation and superior VAD (p= 0.0018), VSD (P= 0.000061), VCI (P= 0.000989) as well as globally (Figure 2).

**Conclusions:** Glaucomatous eyes with a range of no (preperimetric) to severe visual field defects showed significant reduction in macular perfusion parameters as compared to normal eyes. There was a strong correlation of degree of perfusion impairment with degree of corresponding visual field defects in hemifields. This method will likely prove useful in the future for diagnosis, staging and monitoring of glaucoma.
Commercial Relationships: Ingy Madi, Carl Zeiss Meditech (F); Arman Zaman, Carl Zeiss Meditech (F); Amir H. Kashani, Carl Zeiss Meditech (R), Carl Zeiss Meditech (C), Carl Zeiss Meditech (F); Zhongdi Chu, None; Ruikang K. Wang, Carl Zeiss Meditech (R), Carl Zeiss Meditech (C), Carl Zeiss Meditech (F), Carl Zeiss Meditech (P); Grace M. Richter, Carl Zeiss Meditech (F)

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