# A prospective longitudinal study to investigate corneal hysteresis as a risk factor of central visual field progression in glaucoma

Alireza Kamalipour, MD, MPH[1]; Sasan Moghimi, MD[1]; Medi Eslani, MD[1]; Takashi Nishida, MD, PhD[1]; Vahid Mohammadzadeh, MD[1]; Eleonora Micheletti, MD[1]; Christopher A. Girkin, MD[2]; Massimo A. Fazio, PhD[1,2,3]; Jeffrey M. Liebmann, MD[4]; Linda M. Zangwill, PhD[1]; and Robert N. Weinreb, MD[1]

[1]Hamilton Glaucoma Center, Shiley Eye Institute, Viterbi Family Department of Ophthalmology, University of California San Diego, La Jolla, CA.

[2]Department of Ophthalmology and Visual Sciences, Heersink School of Medicine, University of Alabama at Birmingham, AL, United States.

[3]Department of Biomedical Engineering, School of Engineering, University of Alabama at Birmingham, AL, United States.

[4]Bernard and Shirlee Brown Glaucoma Research Laboratory, Department of Ophthalmology, Edward S. Harkness Eye Institute, Columbia University Irving Medical Center, New York, NY

## Abstract

### Purpose

To evaluate the role of corneal hysteresis (CH) as a risk factor of central visual field (VF) progression in a cohort of glaucoma suspect and glaucoma patients

### Methods

In this prospective cohort study, 248 eyes of 143 subjects who were followed for an average of 4.8 years with a minimum of 5 visits with 10-2 and 24-2 VF tests were included. Univariable and multivariable linear mixed effects models were used to identify characteristics associated with the rate of change over time in 10-2 and 24-2 mean deviation (MD). Mixed effects logistic regression was used to evaluate characteristics associated with an increased likelihood of event-based 10-2 VF progression based on clustered pointwise linear regression (PLR) criterion.

### Results

The baseline CH was significantly associated with 10-2 ($P < 0.001$) and 24-2 ($P = 0.044$) VF progression in the univariable trend-based analysis. In multivariable trend-based analyses, each 1 mmHg lower CH was associated with a 0.07 dB/year ($P < 0.001$) faster rate of decline in 10-2 MD. However, the association between lower baseline CH and the rate of 24-2 MD progression was not statistically significant ($P = 0.490$) in multivariable analysis. In multivariable event-based analysis, lower CH was associated with an increased likelihood of 10-2 VF progression (OR = 1.35 per 1 mmHg lower, $P = 0.025$). Similar results were found in eyes with early glaucomatous damage at the baseline (baseline 24-2 MD ≥ -6 dB).

### Conclusion

Lower CH was significantly associated with an increased risk of central VF progression on the 10-2 test grid. Given the substantial influence of central VF impairment on the quality of life, clinicians should consider using CH to assess the risk of progression in primary open angle glaucoma patients including those with early disease.

Table 1. Characteristics associated with the rate of 10-2 MD change over time by univariable and multivariable linear mixed effects model analysis

| Variables | Univariable Model | | Multivariable Model | |
|---|---|---|---|---|
| | β (95 % CI) | *p* value | β (95 % CI) | *p* value |
| Age, per 10 years older | -0.05 (-0.11, 0.01) | 0.102 | -0.02 (-0.09, 0.05) | 0.561 |
| Gender: F/M | 0.13 (0.00, 0.26) | **0.049** | 0.04 (-0.10, 0.18) | 0.586 |
| Race: | | | | |
| African American/ Non-African American | -0.01 (-0.15, 0.13) | 0.889 | -0.02 (-0.17, 0.12) | 0.762 |
| Axial length, per 1mm longer | 0.01 (-0.06, 0.07) | 0.790 | - | - |
| CCT, per 10 µm thinner | 0.00 (-0.02, 0.01) | 0.844 | - | - |
| Self-reported diabetes | -0.07 (-0.25, 0.11) | 0.433 | - | - |
| Self-reported hypertension | 0.06 (-0.08, 0.19) | 0.412 | - | - |
| Baseline systolic blood pressure, per 10 mmHg higher | 0.00 (-0.04, 0.03) | 0.827 | - | - |
| Baseline diastolic blood pressure, per 10 mmHg higher | 0.00 (-0.05, 0.05) | 0.992 | - | - |
| Baseline IOP, per 1 mmHg higher | 0.00 (-0.02, 0.01) | 0.612 | - | - |
| Mean IOP during follow up, per 1 mmHg higher | -0.01 (-0.03, 0.01) | 0.277 | -0.02 (-0.04, 0.00) | **0.043** |
| History of disc hemorrhage | -0.11 (-0.25, 0.02) | 0.096 | -0.12 (-0.25, 0.02) | 0.093 |
| Baseline MD 10-2, per 1 dB worse | -0.01 (-0.02, 0.00) | 0.111 | - | - |
| Baseline PSD 10-2, per 1 dB higher | -0.01 (-0.02, 0.00) | **0.036** | - | - |
| Baseline MD 24-2, per 1 dB worse | -0.02 (-0.03, -0.01) | **0.002** | -0.02 (-0.03, -0.01) | **0.004** |
| Baseline PSD 24-2, per 1 dB higher | -0.02 (-0.03, 0.00) | **0.007** | - | - |
| Baseline CH, per 1 mmHg lower | -0.07 (-0.11, -0.04) | **< 0.001** | -0.07 (-0.11, -0.03) | **< 0.001** |
| Follow up duration, per 1 year longer | 0.04 (-0.04, 0.11) | 0.363 | 0.02 (-0.06, 0.10) | 0.628 |

MD = mean deviation; F = female; M = male; CCT = central corneal thickness; IOP = intraocular pressure; PSD = pattern standard deviation; CH = corneal hysteresis.

Values are shown in β coefficient (95% confidence interval), unless otherwise indicated. Age, Race, mean IOP and clinically independent variables with a *p* value of less than 0.10 in the univariable analysis were included in the multivariable model. Statistically significant *p* values are shown in bold. Negative values correspond to faster MD decline over time.

Table 2. Characteristics associated with the likelihood of event-based 10-2 VF progression defined by clustered pointwise linear regression criteria of mean sensitivity using univariable and multivariable mixed effects logistic regression analysis

| Variables | Univariable Model | | Multivariable Model | |
|---|---|---|---|---|
| | Odds ratio (95 % CI) | *p* value | Odds ratio (95 % CI) | *p* value |
| Age, per 10 years older | 0.98 (0.65, 1.48) | 0.937 | 0.87 (0.60, 1.27) | 0.472 |
| Gender: F/M | 0.57 (0.23, 1.43) | 0.232 | 0.67 (0.21, 2.08) | 0.486 |
| Race: | | | | |
| African American/ Non-African American | 1.11 (0.41, 2.99) | 0.844 | 1.31 (0.45, 3.82) | 0.616 |
| Axial length, per 1mm longer | 0.93 (0.68, 1.27) | 0.633 | - | - |
| CCT, per 10 µm thinner | 0.99 (0.89, 1.11) | 0.882 | - | - |
| Self-reported diabetes | 1.49 (0.48, 4.65) | 0.490 | - | - |
| Self-reported hypertension | 0.51 (0.21, 1.27) | 0.150 | - | - |
| Baseline systolic blood pressure, per 10 mmHg higher | 0.97 (0.79, 1.19) | 0.772 | - | - |
| Baseline diastolic blood pressure, per 10 mmHg higher | 1.03 (0.71, 1.49) | 0.870 | - | - |
| Baseline IOP, per 1 mmHg higher | 0.97 (0.88, 1.08) | 0.636 | - | - |
| Mean IOP during follow up, per 1 mmHg higher | 1.02 (0.90, 1.15) | 0.805 | 1.05 (0.92, 1.21) | 0.444 |
| History of disc hemorrhage | 2.60 (0.99, 6.82) | 0.052 | 2.23 (0.66, 7.46) | 0.194 |
| Baseline MD 10-2, per 1 dB worse | 1.04 (0.97, 1.12) | 0.242 | - | - |
| Baseline PSD 10-2, per 1 dB higher | 1.08 (0.99, 1.18) | 0.101 | - | - |
| Baseline MD 24-2, per 1 dB worse | 1.08 (1.01, 1.16) | **0.024** | 1.09 (1.00, 1.18) | **0.045** |
| Baseline PSD 24-2, per 1 dB higher | 1.10 (1.00, 1.20) | **0.041** | - | - |
| Baseline CH, per 1 mmHg lower | 1.35 (1.09, 1.67) | **0.006** | 1.35 (1.04, 1.75) | **0.025** |
| Follow up duration, per 1 year longer | 1.14 (0.73, 1.78) | 0.564 | 1.18 (0.75, 1.85) | 0.475 |

MD = mean deviation; F = female; M = male; CCT = central corneal thickness; IOP = intraocular pressure; PSD = pattern standard deviation; CH = corneal hysteresis.

Values are shown in β coefficient (95% confidence interval), unless otherwise indicated. Age, Race, mean IOP and clinically independent variables with a *p* value of less than 0.10 in the univariable analysis were included in the multivariable model. Statistically significant *p* values are shown in bold.

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Title: Using large scale visual field data from clinics in England to examine associations between socio-economic status, late diagnosis, and rapid progression in glaucoma

Authors: Mehal Rathore, Stephen R. Kelly, Giovanni Montesano, Peter Reddingius, David P. Crabb

PURPOSE

The link between deprivation and late diagnosis of glaucoma has been well described. We aim to confirm this association using extensive visual field (VF) data from glaucoma clinics in England and to test the hypothesis that socio-economic status (SES) is associated with rapid VF progression in glaucoma.

METHODS

Anonymised Humphrey VFs were retrospectively extracted from electronic medical records (EMRs) from five regionally different clinics in England in 2015, resulting in 602439 records from 73994 people. Index of Multiple Deprivation (IMD; a standard UK government measure for SES) calculated from residential postcodes within the EMR was available for many of these records. We included adults with ≥2 reliable VF records and used a criterion of Mean Deviation (MD) worse than −12 dB in the worse eye as a surrogate definition for a patient having *advanced VF loss* at diagnosis. We calculated speed of VF loss in patients with ≥6 VFs and used a criterion of worse than -1 dB per year to define a patient as having *rapid VF progression* during follow-up. Patients were grouped into deciles of IMD and percentage of patients with the criterion were calculated.

RESULTS

There was a clear association between IMD and having *advanced VF loss* at diagnosis. For example,18% (291/1616) and 11% (765/6951) of patients had *advanced VF loss* at diagnosis in the most and least deprived IMD decile respectively. The age-corrected odds ratio (OR) for having *advanced VF loss* at entry into hospital eye service was 1.42 (95% confidence interval [CI] 1.21 to 1.67) and 0.75 (95% CI: 0.66 to 0.85, $p<0.001$) in the most and least deprived IMD decile respectively (reference=fifth decile in all cases).The proportion of patients having the attribute of *rapid VF progression* during follow-up did not differ greatly across the SES spectrum with, for example, an age-corrected OR of 1.25 (95%CI: 0.89 to 1.73) and 0.86 (95% CI 0.68 to 1.09) in the most and least deprived IMD decile with both values not differing significantly from the reference value of one ($p =0.19$ & $p =0.22$)

CONCLUSION

Large-scale VF data from English glaucoma clinics supports the claim that SES is associated with glaucoma severity at presentation to hospital eye services in England. However, we found no evidence to support the idea that SES is associated with a greater likelihood of having rapid VF progression during follow-up. The latter hints at equity of glaucoma care once patients are in hospital eye services in England.

There is no conflict of interest.

Author affiliations:

1. Mehal Rathore, City, University of London
2. Stephen R. Kelly, City, University of London
3. Giovanni Montesano, City, University of London
4. Peter Reddingius, City, University of London
5. David P. Crabb, City, University of London

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# Power to the People: Estimating the Detectability of Change in Individual Patients' Visual Field Series

Fabian SL Yii,[1,2] Iván Marín-Franch,[3,2] Paul H Artes [2,4]

1. Centre for Clinical Brain Sciences, University of Edinburgh, UK
2. Southwest Eye Institute, Tavistock, UK
3. Computational Optometry, Atarfe, Spain
4. University of Plymouth, UK

**Purpose:** An unsolved problem with visual field progression is how to interpret negative results. "No significant change" can mean either that there was no meaningful change (evidence of absence) or that the data are insufficient to demonstrate a change (absence of evidence). Here, we describe an approach to help distinguish between these scenarios.

**Methods:** Our approach is based on Monte-Carlo simulation: An individual patient's series of visual fields is modified by adding an artificial "progression signal" to the observed thresholds, and the modified series is then analyzed for change. Repeated many times with randomly selected visual field locations making up the progression signal, this can be used to assess the statistical power of an individual patient's progression analysis. In other words, the proportion of positive outcomes (i.e. statistically significant progression) indicates how well change of a particular magnitude can be identified in the visual field series. We explored this technique in data from a study where 30 patients with stable glaucoma underwent many visual field tests over a short period (Artes et al, 2014). For each patient, series of 5 visual field tests were evaluated. Simulated progression signals (expressed as rates of change in Mean Deviation, dB/y) were varied from -4.0 dB/y (catastrophic progression) to -0.05 dB/y (negligible progression).

**Results:** The curves describing the relationship between strength of the progression signal and power were sigmoidal and of similar shape between patients (Figure 1). The power associated with a progression signal of -1 dB/year varied substantially between patients, between 24% and 100%. The progression signal associated with a power of 80% varied by a factor of >10 between patients, from approximately -0.25 dB/y to -3.50 dB/y.

**Conclusions:** Our results confirm that there is a large variation between patients as to the detectability of true change. In some patients' visual field series the power to detect even catastrophic change (as negative as -2.0 dB/y) was low. Our technique is a logical extension of Permutation of Pointwise Linear Regression (PoPLR) and will be made available in the open source R package "visualFields".

**Conflicts of interest:** None of the authors report a conflict of interest with this work.

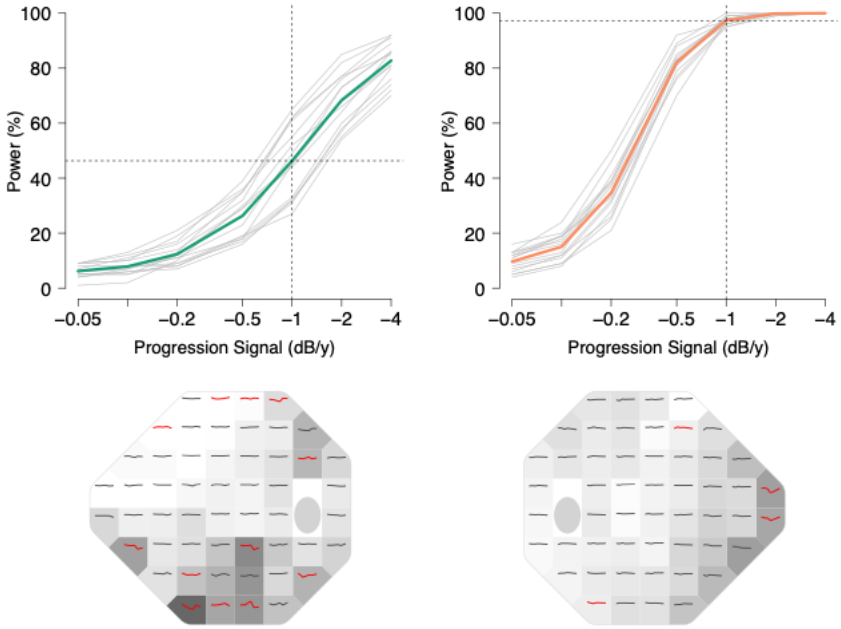


*Figure 1: Power curves (top) and corresponding visual field series (bottom) of two selected patients.*

Title: Measurement of fixational eye movements during visual field testing

Takuya Ishibashi[1]; Chota Matsumoto[1]; Hiroki Nomoto[1]; Fumi Tanabe[1]; Shinji Kimura[2]; Shunji Kusaka[1]
1. Department of Ophthalmology, Kindai University, Faculty of Medicine
2. CREWT Medical Systems, Inc.

Purpose: Although visual field testing is conducted with the subject gazing at a fixation target, constant minute eye movements, called fixational eye movements, do occur during fixation. We examined dynamic changes in fixational eye movements associated with stimulus presentation during visual field testing.
Methods: We used the head-mounted perimeter imo®, which is capable of measurement under binocular conditions, with the frame rate of its fixation monitoring camera improved to 300 Hz, to assess fixational eye movements in 18 healthy individuals. All subjects underwent visual field testing under binocular and monocular conditions three times each. The period of before and after the stimulus presentation is divided into five 200-msec time windows for analysis: stimulus presentation, before stimulus presentation 2 (b2), before stimulus presentation 1 (b1), after stimulus presentation 1 (a1), and after stimulus presentation 2 (a2). We measured changes in fixational eye movements during testing under monocular and binocular conditions and analyzed these changes based on the bivariate contour ellipse area (BCEA). We also assessed the changes in the horizontal and vertical microsaccade rates separately.
Results: The BCEA and vertical microsaccade rates throughout b2−a2 were significantly lower in the binocular condition than in the monocular condition ($p < 0.01$, $p < 0.05$, respectively). Additionally, the BCEA and vertical microsaccade rates during stimulus presentation were significantly lower in the binocular condition than in the monocular condition ($p < 0.05$, $p < 0.01$, respectively). There was no significant difference in the horizontal microsaccade rate between the binocular and monocular conditions. Considering the BCEA, the retinal area stimulated by the test target during stimulus presentation under monocular conditions was 0.329 degrees$^2$, which was roughly twice that of the original stimulus size (Goldmann size III: 0.43° visual angle).
Conclusions: Fixational eye movements during stimulus presentation may affect threshold variability in test locations. Visual field testing under binocular conditions suppresses fixational eye movements, especially vertical microsaccade rates, and is a useful method for stabilizing fixation during testing.

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# Moving vs. Static Stimuli for Perimetry: Patient Experience

Donovan Redtomahawk, Cindy Albert, Steven L Mansberger, Stuart K Gardiner

Devers Eye Institute, Legacy Health, Portland, OR, USA

## Purpose

Standard automated perimetry is fatiguing and frustrating for patients, which reduces repeatability and reliability of the results. This is partly because it requires concentrating for several minutes; and a large proportion of stimuli are unseen (especially in glaucoma patients) leading to extended gaps during which nothing appears to happen. Additionally, at damaged locations the frequency-of-seeing curve flattens. This not only increases variability, but also increases the proportion of stimuli where the patient is unsure whether they saw the stimulus or not, potentially adding to their frustration. We hypothesize that using moving stimuli will steepen the frequency of seeing curve, reducing this uncertainty and consequent frustration, and hence increasing patient satisfaction with the test.

## Methods

A Size V moving stimulus was programmed using the Open Perimetry Interface to travel parallel to the average nerve fiber bundle orientation at each location, at speed proportional to the average local magnocellular ganglion cell spacing (Fig 1). This was then compared against an otherwise identical stationary stimulus. First, frequency-of-seeing curves were collected for both moving and static stimuli at 4 locations in 10 individuals, on an Octopus perimeter. Next, 34 locations in 148 glaucoma patients / suspects were tested using both stimuli (in random order), with the same ZEST seen / not seen algorithm lasting around 5 minutes for each stimulus type. Participants were then asked for their preference between the two tests.

## Results

Among the 40 locations at which frequency-of-seeing curves were collected, the moving stimulus gave higher sensitivity at 39 locations, and lower inter-quartile range at 33 locations (Fig 2). Among the 148 participants who underwent clinically-realistic ZEST testing, 50% of subjects stated preferring the moving stimulus, vs. 24% who preferred the static stimulus.

## Conclusions

Using a moving stimulus for perimetry increases sensitivities and reduces variability compared to static stimuli. This appears to make the test more tolerable for patients. We hypothesize that this facilitates concentration during the test, leading to a further reduction in long-term variability. Use of moving stimuli increases patient satisfaction, while simultaneously allowing reliable testing at locations with more severe glaucomatous damage.

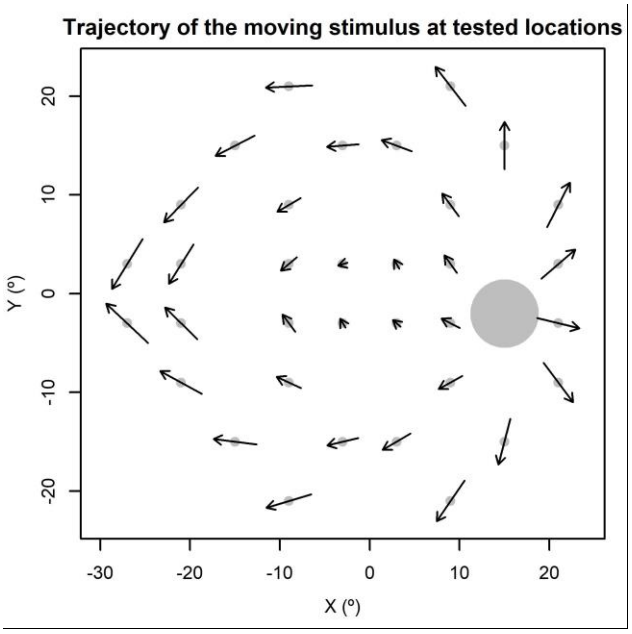
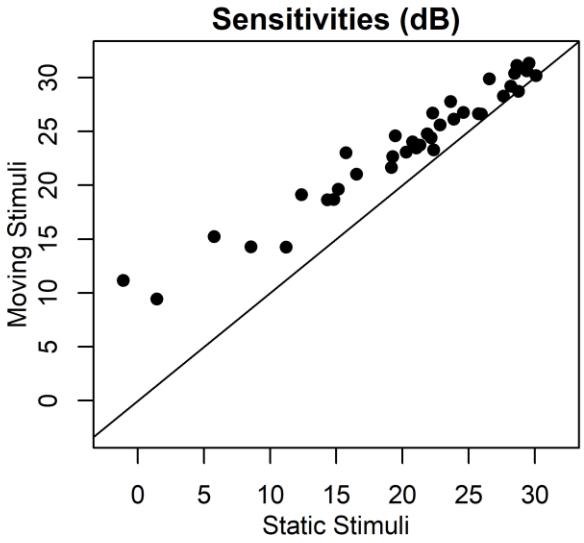

Trajectory of the moving stimulus at tested locations
Y (°)
X (°)
20
10
0
-10
-20
-30
-20
-10
0
10
20

Fig 1



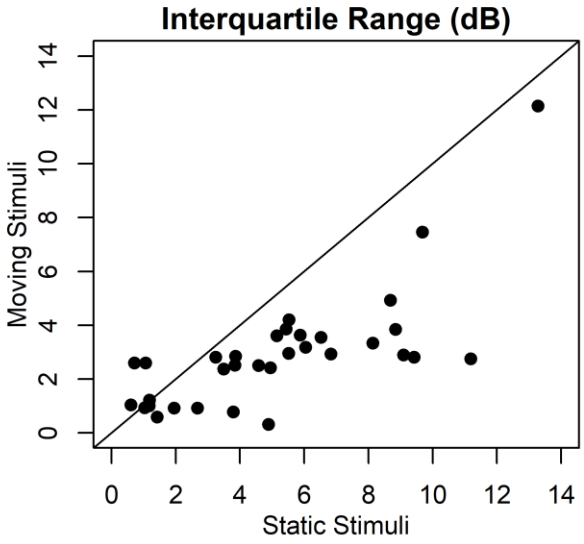




Fig 2

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POSTER ONLY

# Moving vs. Static Stimuli for Perimetry: Repeatability and Defect Detectability

Stuart K Gardiner, Cindy Albert, Donovan Redtomahawk, Steven L Mansberger

Devers Eye Institute, Legacy Health, Portland, OR, USA

## Purpose

Using static automated perimetry, pointwise sensitivities below ~15-19dB are unreliable due to excessive variability. Allowing the stimulus to move parallel to the nerve fiber bundles increases sensitivities, especially at damaged locations, while still assessing damage within the same arcuate region. Here, we test the effect on repeatability and detectability of defects.

## Methods

171 participants were tested using both static stimuli (Size V) and moving stimuli (also Size V, moving parallel to the average nerve fiber bundle orientation at each location, with speed proportional to local magnocellular ganglion cell spacing), in random order. 34 locations were tested using an otherwise identical seen / not seen ZEST algorithm on a clinical perimeter. 23 participants had healthy vision, and were used to derive rates of age-related change and normative limits for each location; 148 were glaucoma patients / suspects, of whom 80 were retested 6 months later.

## Results

Average Mean Deviations from SITA Standard static perimetry were -0.1dB for the healthy eyes, and -3.1dB for glaucomatous eyes (range -20.0 to +2.3dB). Sensitivities for moving stimuli were higher (Fig 1A), reducing the proportion below 15dB from 6.6% to 3.2%; and test-retest limits of agreement were narrower (-6.3 to +6.4dB vs. -13.1 to +7.8dB, Fig 1B/1C). More locations were outside age-corrected 95% normal limits for static stimuli (27.1%) than for moving stimuli (18.6%). However, the age corrections derived from 23 healthy eyes varied greatly between locations for static stimuli, as seen by the regression lines for each location (Fig 2, top). Thus, the proportions outside age-corrected normal limits also varied more between pairs of neighboring locations (Fig 2, middle and bottom).

## Conclusions

Using a moving stimulus for perimetry increases sensitivities, so locations remain within the dynamic range longer; and reduces variability. It is possible that it is harder to detect defects with moving stimuli, but this remains unclear, because the high variability of static stimuli makes age corrections inaccurate. However, this issue could easily be circumvented by having stimulus speed increase with contrast such that early detection would be unaltered. Moving stimuli enable reliable testing at more severely damaged locations than is currently possible.

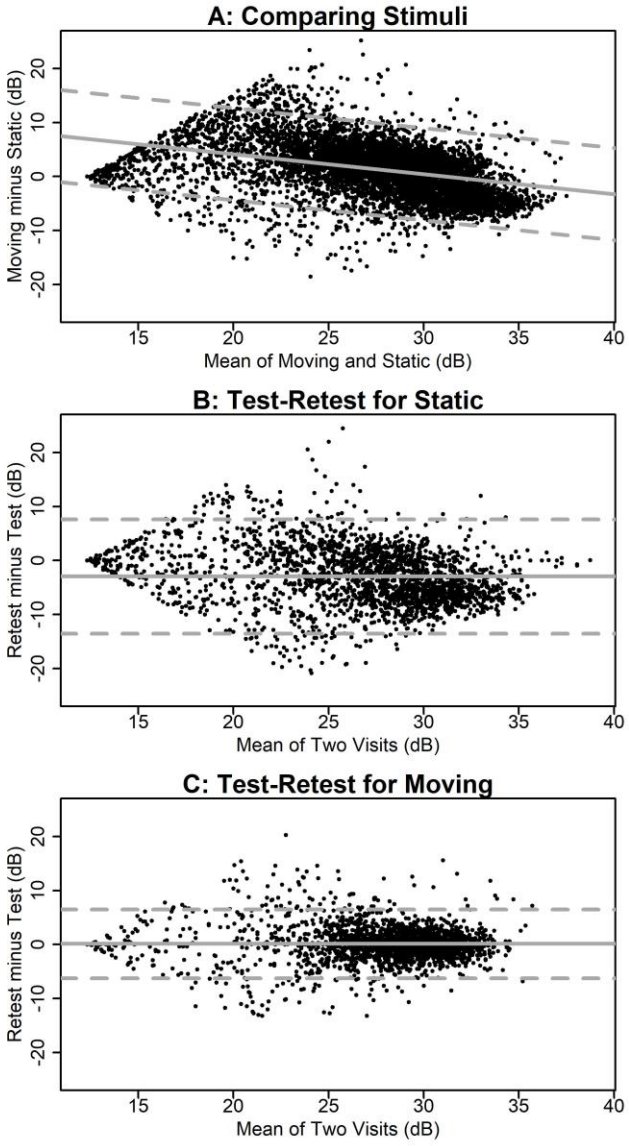
A: Comparing Stimuli
Moving minus Static (dB)
Mean of Moving and Static (dB)
B: Test-Retest for Static
Retest minus Test (dB)
Mean of Two Visits (dB)
C: Test-Retest for Moving
Retest minus Test (dB)
Mean of Two Visits (dB)

Fig 1

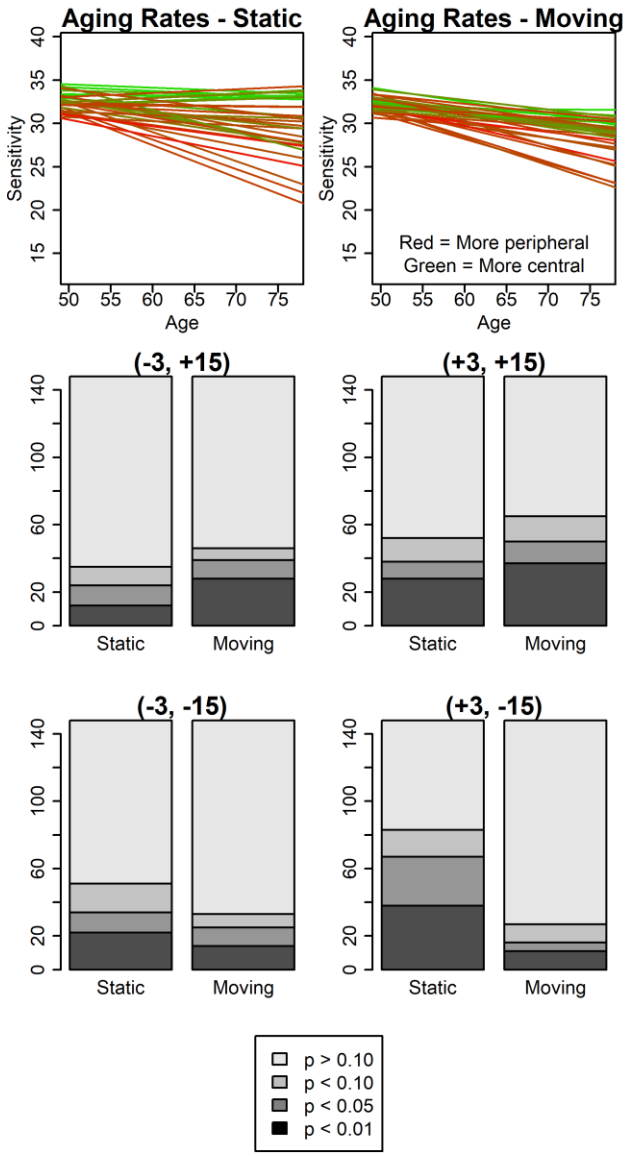


Fig 2

Disclosures:
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DR: None
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