RESEARCH ARTICLE

Morphology and Repeatability of Automated Perimetry using Stimulus Sizes III, V and VI

Authors
Michael Wall*§ and Chris A. Johnson*
Affiliations
Departments of Ophthalmology* and Neurology§
University of Iowa, College of Medicine
Veterans Administration Hospital, Iowa City, IA
Automated Perimetry with Sizes V and VI
Correspondence
Michael Wall, M.D.
University of Iowa, College of Medicine
Department of Neurology
200 Hawkins Drive #8820-23
Iowa City, IA 52242-1053
319-356-8758 (voice), 319-356-4505 (fax)

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Abstract
The purpose of this study is to describe the visual field morphology and the repeatability of normal participants using Humphrey perimetry with stimulus sizes III, V and VI. We tested one eye of 60 ocular healthy participants with the Humphrey perimeter using sizes III (0.43°) SITA Standard, V Full Threshold (1.72°) and VI Full Threshold (3.44°) stimuli. The patients were retested 1-4 weeks later. We compared the mean scores, eccentricity zones, and point-wise sensitivities among the sizes and their retest variability. Repeated measures ANOVA on Ranks was performed with the dependent variable as sensitivity (dB) of average sensitivity of each eccentric zone. The mean sensitivities (average of the two visits) were sizes III: 30.16 ± 1.1, V: 34.4 ± 1.0 and VI 36.0 ± 1.0 ($p < 0.001$ with all Tukey post hoc paired comparisons significant). Significant differences between the groups were also present for each eccentric zone except 0° for size V vs. size VI. The mean difference on retest across test locations was 0.26 dB for size III, 0.26 dB for size V, and 0.27 dB for size VI indicating minimal learning effect. The difference in variability between sizes III, V and size VI increased with eccentricity, with size III increasing more than the larger stimulus sizes but statistical significance for this difference was not reached. In this investigation, we found with increasing stimulus size, the visual field morphology flattens, and the retest variability becomes slightly less for stimulus sizes V and VI full threshold testing compared with size III SITA standard results.

Keywords: perimetry, visual testing, visual field, spatial summation, stimulus size

1. Introduction

Since the introduction of the Goldmann perimeter in 1945, most manual and automated perimetry have used the six stimulus sizes of Goldmann's design. In particular, automated perimetry has standardized on the mid-range (4 mm^2, 0.43°) Goldmann stimulus size III. This was chosen as a compromise between the susceptibility of small sizes to refractive blur and possible loss of spatial resolution with large-sized stimuli. However, as visual field damage progresses, the limited effective dynamic range using size III stimuli becomes obvious.[1-3] In addition, lower retest variability can be achieved by using size V stimuli rather than size III.[1, 4, 5]

We have reported frequency of seeing curves of glaucoma patients that were generated by using a custom test program to test patients at 2 dB intervals over a 2-3 log unit range. The patients were tested with size III and size V stimuli in areas of normal sensitivity and areas of 10-20 dB loss. The same test locations were used in the same session for both sizes. As shown by a steepening of the slope of the frequency of seeing curve, variability substantially decreased in the glaucoma patients with 10-20 dB loss when the size V stimulus was used. These findings of lower variability have led some to use size V stimuli in conventional automated perimetry to follow patients with moderate to severe visual loss[6, 7] and as an outcome measure in clinical trials. However, there is limited empirical data available regarding the topographic differences, normative limits and retest variability among Goldmann sizes III, V and VI with standard automated perimetry using the Humphrey Field Analyzer.

Wilensky and coworkers performed size V testing on 18 glaucoma patients that failed to respond to the 0 dB stimulus on the Octopus perimeter. They found many instances of patient responding to the larger stimulus in areas blind to the size III stimulus. They postulated spatial summation as the mechanism responsible for their findings. Thus, the dynamic range of standard perimetry could be expanded by using a larger stimulus size.[6, 7]

Choplin et al. studied 17 normal participants and 31 patients with glaucoma or ocular hypertension with the Octopus perimeter comparing sizes III, IV and V and investigated the effect of change in stimulus size on sensitivity.[8] They employed a custom program of 22 test locations in an hour glass pattern; ten test locations had two threshold determinations. They found mean retinal sensitivities with sizes III, IV and V of 28.4, 31.9 and 36.0 dB respectively. The 7.6 dB increase in sensitivity from size III to size V was said to be fairly uniform across the visual field. Most importantly, fluctuation on retest was greatest for size III (2.0 db) and least for size V (1.55 dB). These findings, however, are only indirectly comparable to those on the Humphrey Field Analyzer (HFA) as the Octopus perimeter employs a background of 4 asb as opposed to the 31.5 asb background of the Humphrey perimeter and the presentation time is 100 msec in contrast to the 200 msec of the HFA.

Zulauf and Caprioli [6] studied 49 eyes of 49 glaucoma patients with stimulus sizes III and V using the Octopus perimeter. They reported that scotomas were shallower with size V and the pattern of defects was better represented by using size III. Due to the greater dynamic range of size V stimuli, they concluded that stimulus size V should be used if more than 10% of test locations have absolute scotomas or the mean sensitivity falls below 15 dB with stimulus size III. However, empiric probability plots were not used and no gray scale adjustments were made.

We computed empiric probability plot percentile limits for size III (SITA) and size V (Full Threshold) and then compared probability plots of 120 glaucoma patients tested in the same way with these two stimulus sizes and methods. We compared the number of abnormal test locations and found a similar number of abnormal test locations (no significant difference) for the size III and size V testing conditions identified by the probability plots.[1, 9] Surprisingly, in glaucoma patients, using the large size V stimulus did not reduce the sensitivity to detect visual field defects. This has been confirmed in subsequent studies.[10, 11]

Kalloniatis, Phu and coworkers, in a series of experiments[12-14] have studied a range of stimulus sizes and effects on defect detection and have concluded stimuli operating within complete spatial summation detect more and deeper defects. This requires the stimulus size be changed for varying amounts of visual field damage and visual field eccentricity.

The normal visual field to size III stimuli has been well studied using both full threshold testing[15, 16] and the Swedish interactive threshold algorithm (SITA).[17-19] While the sensitivity values are 1-2 dB higher for Size III SITA compared to size III full threshold testing, as Artes et al. have shown,[20] the retest variability of the two tests is nearly identical except for small differences at the tails of the testing range. However, there is limited data available on the normal static threshold automated visual field to sizes V and VI stimuli and their retest variability using the HFA. Since sizes V and VI stimuli have a broader dynamic range, lower variability and are increasingly used in glaucoma patients, we thought study of the relationship of these larger sizes with size III stimuli and data on the visual field morphology of the larger sizes would be important for visual field interpretation. Therefore, we tested a group of normal participants twice within two months with SITA Standard size III testing and Full Threshold sizes V and VI perimetry to compare the outcomes and repeatability. We also tested a group of normal participants once a week for 5 weeks with size III SITA and size III full threshold testing to compare these two methods to better interpret the differences in methods.

2. Methods

Participants: The visual testing protocol was approved by the University of Iowa Institutional Review Board. The tenets of the Declaration of Helsinki were followed. Sixty ocular normal participants were tested at baseline and again at a separate sitting within 1-8 weeks with most patients retested within one month. They all gave written informed consent to participate in the study. The normals were volunteers paid in agreement with the Institutional Review Board. The participants answered advertisements inviting them to participate in research. The average age was 61.22 ± 8.92 with a range of 42 – 79. Thirty-eight of the volunteers were women and 22 were men.

Participants were considered normal if they had 1) no history of eye disease except refractive error (no more optical correction than five diopters of sphere or three diopters of cylinder distance correction), 2) no history of diabetes mellitus or systemic arterial hypertension, 3) a normal ophthalmologic examination including 20/25 or better Snellen acuity, and 4) normal automated perimetry results (Humphrey Visual Field Analyzer, program 24-2). The participants either had undergone a complete eye exam within 12 months prior to this study or were examined by an ophthalmologist on the day of testing to ensure normal ocular health.

Visual Testing: All participants underwent testing with size III stimuli using the SITA standard 24-2 algorithm first followed by testing with sizes V and VI stimuli. The size III stimulus area is 4 mm^2 or 0.43° diameter, the size V area is 64 mm^2 or 1.72° diameter and the size VI is 3.44° diameter and 256 mm^2. Since there is no SITA strategy available for sizes V and VI stimuli, the participants were tested with Humphrey 24-2 Full Threshold testing for size V. These are the strategies that are commonly clinically used. We followed the manufacturer's recommendations and used a corrective lens when necessary. Care was taken to prevent lens rim artifact. The participants had testing in one eye, chosen at random, but the same eye was used for all tests. All visual field examinations met the following reliability criteria: fixation losses less than 20% or normal gaze tracking, false positive rate < 10% and false negative rate < 33%.

As noted above, we compared size III SITA with size V and VI full threshold testing. Since it is also important to compare size III full threshold testing with size V full threshold testing, we tested 5 normal participants once a week for five weeks across decades with size III full threshold, size III SITA and size V full threshold testing and compared the retest results. Our data confirm a 1-2 dB increase in sensitivity for SITA testing (Figure 1 top row) but minimal if any differences in repeatability (Figure 1 bottom row).

Figure 1.

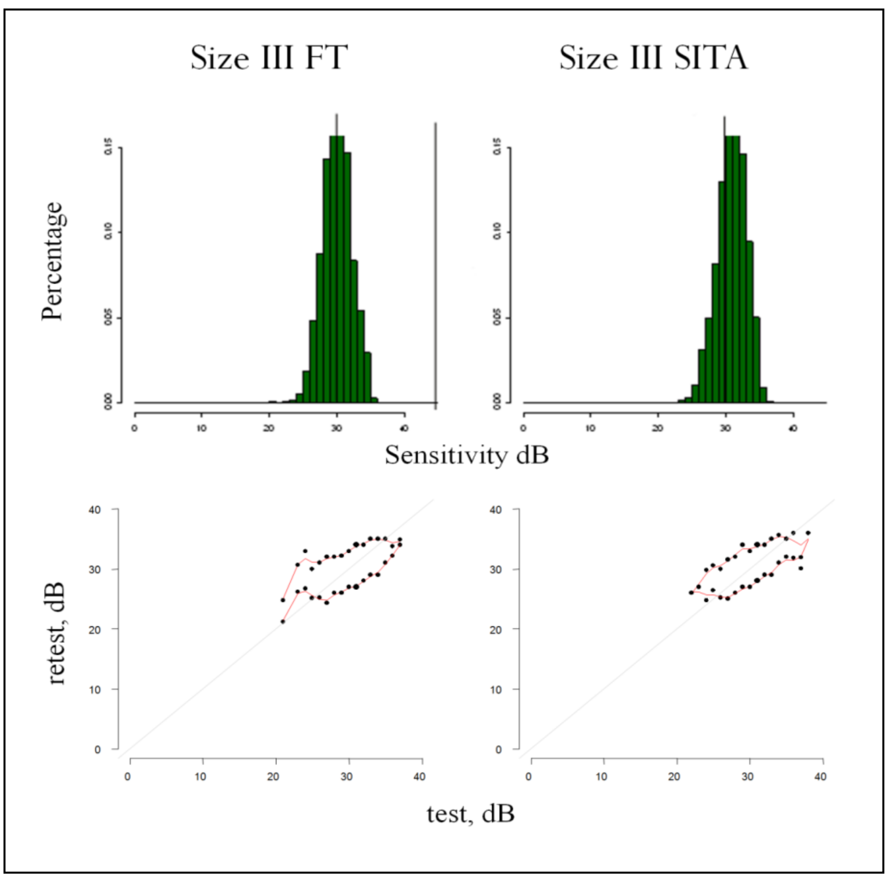

Figure 1. A comparison of retest variability of size III full threshold, size III SITA in 5 normal participants tested once a week for 5 weeks. The graphs at the top s how histograms of the cumulative sensitivities; note the slightly higher sensitivity of SITA testing but the otherwise very similar distributions. The graphs at the bottom show the 95th percentile of the retest values for the three testing methods. Note the similarity of size III full threshold and size III SITA.

<u>Statistical Analysis</u>: Repeated measures analysis of variance (ANOVA) was used to compare sensitivities and variability between the two tests. Two 4 x 2 (zone, test) repeated measures ANOVA were used to test for eccentric zone effects. The zones were five areas about 6° apart with values from the blind spot (15, 3 and 15, -3) excluded. Zone 1 was the innermost and zone 5 the outermost area. Outcome measures were mean sensitivity (dB average between visit 1 and visit 2, at each location, for each test) and variability (dB difference between visit 1 and visit 2, at each location, for each test). We also examined the effect of age on sensitivity with linear regression. An alpha level of 0.05 was set to determine statistically significant differences.

3. Results

The average threshold for the three stimulus sizes are found in Table 1. The mean sensitivities (average of the two visits) were sizes III 30.16 +/- 1.1, V: 34.4+/- 1.0 and VI 36.0 +/- 1.0. Note the increasing sensitivity with increasing stimulus size; these differences were statistically significant ($p < 0.001$ with all Tukey post hoc paired comparisons significant).

The differences in eccentricity, by concentric zone, are found in Table 2 and Figure 2. Significant differences between the groups were also present for each eccentric zone except 0° for size V vs. size VI.

Figure 2.

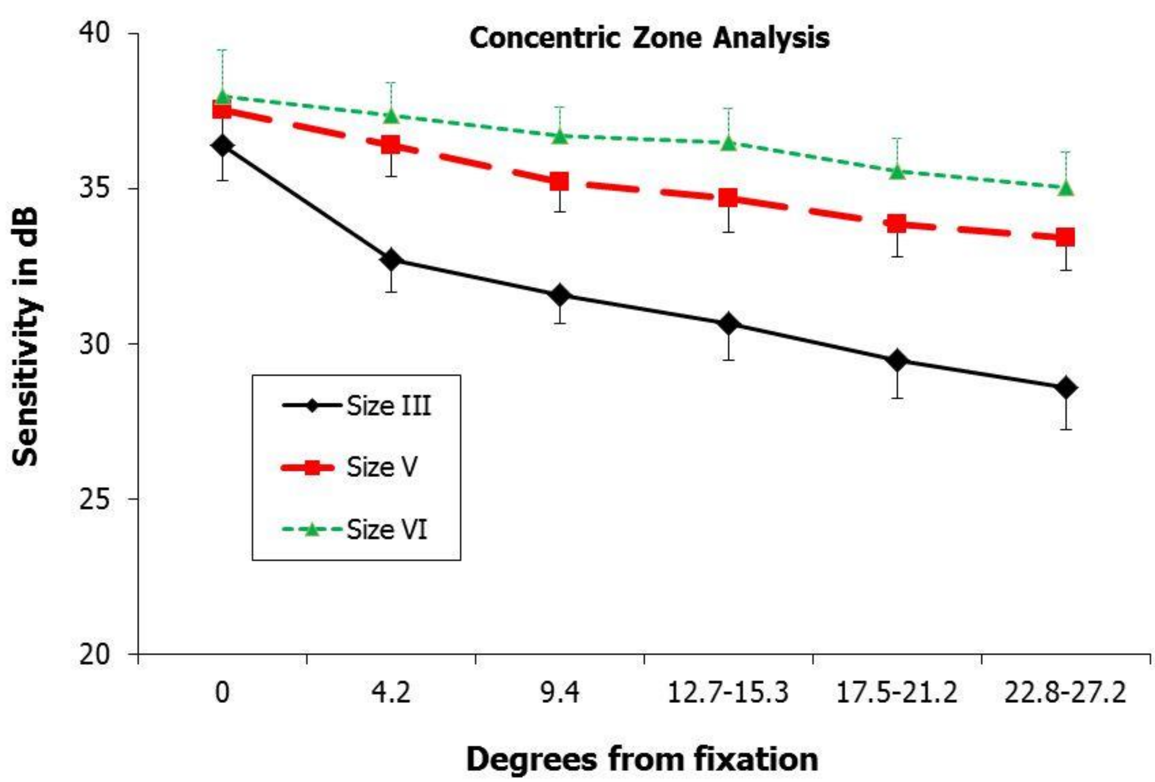

Figure 2. Mean of the test and retest of the fovea and 5 concentric zones comparing size III (black) and size V (red) and size VI (green); error bars represent one standard deviation.

Table 1. Descriptive statistics for participants in the study. (v = visit)

	Mean Threshold					
	Size III v1	Size III v2	Size V v1	Size V v2	Size VI v1	Size VI v2
Average	30.03	30.29	34.22	34.48	35.60	35.87
Standard Dev.	1.16	1.33	1.10	1.16	1.11	1.11
Median	30.01	30.21	34.25	34.43	35.72	36.00
Minimum	26.90	25.04	31.75	32.38	32.85	32.94
Maximum	32.46	32.23	36.85	38.42	37.56	37.83

Table 2. Means and standard deviations of the normal participants comparing the tests by eccentric zone.

Eccentric Zone	**Size III**		**Size V**		**Size VI**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Fovea	36.39	1.12	37.55	1.34	37.98	1.49
Central	32.70	1.02	36.39	1.02	37.34	1.09
Paracentral	31.58	0.92	35.23	1.00	36.68	0.93
Mid-peripheral	30.68	1.21	34.70	1.12	36.47	1.11
Peripheral	29.49	1.25	33.84	1.03	35.56	1.04
Far Peripheral	28.59	1.34	33.41	1.05	35.03	1.12

In these healthy ocular observers, the mean difference on retest across test locations (learning effect) was minimal (0.26 dB for size III, 0.26 dB for size V and 0.27 dB for size VI. The difference in variability between size V and size VI increased with eccentricity (interaction was significant: $p<.001$). Figure 3a,b shows the pointwise means and standard deviations adjusted for age 45 for sizes III and V and Figure 4c shows the comparable values used as "normal" by the HFA, also for age 45. Figure 3d shows the means and standard deviations for size VI. Figure 4 depicts the retest difference by plotting test 1 sensitivity against those for test 2 by stimulus size; note the lower variability using size V stimuli. Figure 5 shows the retest histograms (top) and the 5th to 95th confidence interval for the tests retest values (bottom). Note how comparisons of figures 2-4 show the higher sensitivities and lower variabilities with increasing stimulus size. The change in foveal sensitivity with age is shown by the equation (S_a is sensitivity estimated for age): $S_a = -0.04(\text{age}) + 39.4$; $r^2 = 0.075$ for size III, $S_a = -0.07(\text{age}) + 41.5$; $r^2 = 0.16$ for size V and $S_a = -0.052(\text{age}) + 41.2$; $r^2 = 0.1$. For the full field excluding the fovea these values were $S_a = -0.05(\text{age}) + 32.9$; $r^2 = 0.17$ for size III, $S_a = -0.06(\text{age}) + 37.3$; $r^2 = 0.24$ for size V and $-0.05(\text{age}) + 39.05$; $r^2 = 0.19$ for size VI. Therefore, there is little difference in the effect of age between the three stimulus sizes for foveal sensitivity.

Figure 3a. Test 2

			28.0	28.1	27.6	27.3		
			2.4	3.0	2.6	3.2		
		29.4	29.9	30.3	29.5	29.7	29.3	
		2.1	1.9	2.1	2.0	1.8	2.2	
	29.3	30.5	31.5	31.4	30.8	30.2	30.3	29.2
	2.1	2.2	1.9	1.8	1.8	1.8	2.0	2.2
28.1	29.7	31.4	32.3	33.0	32.5	31.6	26.7	29.9
2.1	1.7	1.6	1.4	1.5	1.5	1.6	4.5	2.4
27.7	29.9	31.5	32.6	32.9	32.9	31.7	3.2	29.9
2.5	2.0	1.7	1.5	1.6	1.3	1.8	6.0	2.7
	29.3	31.0	31.7	31.6	31.4	31.2	30.8	29.9
	1.9	1.5	1.7	1.8	1.6	1.8	1.7	2.2
		29.9	30.3	30.5	30.4	30.6	30.2	
		1.8	2.0	1.9	1.9	1.5	2.4	
36.3 fovea								
1.2			28.9	29.0	29.7	29.4		
			2.2	2.3	2.8	2.7		

Figure 3b. Test 2

			32.7	32.8	32.1	32.4		
			1.8	2.0	1.6	2.0		
		33.7	33.8	34.0	33.2	33.8	33.1	
		1.7	1.7	1.6	1.8	1.6	1.7	
	33.4	34.2	35.3	35.2	34.7	34.5	34.0	33.6
	1.7	1.5	1.5	1.7	1.8	1.6	1.8	1.6
33.1	34.0	34.9	35.6	36.2	36.1	35.2	32.7	34.1
1.7	1.6	1.7	1.6	1.3	2.0	1.7	2.6	1.5
33.2	34.5	35.3	36.1	36.8	36.7	35.4	14.8	34.2
1.9	1.8	1.7	1.5	1.2	1.4	1.9	7.6	1.6
	34.0	34.8	35.9	35.2	35.4	35.6	34.5	34.2
	1.9	1.9	1.6	2.1	1.7	1.6	1.8	1.8
		34.3	34.7	34.8	35.0	34.7	34.9	
		1.5	1.9	1.7	1.8	1.8	1.6	
37.9 fovea								
1.7			34.4	34.0	34.4	34.6		
			1.7	1.8	1.8	1.8		

Figure 3c. Size V values in Humphrey Field Analyzer for age 45

			30	30	30	30		
		30	31	31	31	31	30	
	30	31	32	32	32	32	31	30
29	30	31	32	33	33	32	31	30
29	30	31	32	33	33	32	31	30
	30	31	32	32	32	32	31	30
		30	31	31	31	31	30	
			30	30	30	30		

Figure 3d. Test 2

			34.6 2.0	34.9 1.5	34.1 1.7	34.1 1.7		
		35.1 1.6	35.4 1.5	35.8 1.6	35.0 1.9	35.5 1.7	35.1 1.6	
	35.0 1.6	35.8 1.7	37.3 1.7	36.6 1.7	35.9 1.6	36.7 1.6	35.6 1.3	35.2 1.8
34.7 1.7	35.3 1.8	36.8 1.9	37.1 1.5	37.1 1.6	37.3 1.9	36.7 1.6	34.9 1.7	35.6 1.7
34.5 1.8	36.1 1.9	37.1 1.8	37.1 1.5	37.4 1.3	37.5 1.4	37.1 1.5	23.6 7.2	35.8 1.6
	35.5 1.8	36.6 1.5	37.8 1.5	36.8 1.8	37.1 1.7	37.1 1.8	35.8 1.5	35.7 1.6
		36.0 1.4	36.2 1.6	36.2 1.6	36.2 1.7	36.5 1.6	36.2 1.7	
38.1 fovea 1.7								
			35.9 1.5	35.7 1.6	35.8 1.6	36.0 1.7		

Figure 3. (a) Size III mean of two tests and interindividual standard deviation corrected to age 45; (b) Size V mean of two tests and interindividual standard deviation corrected to age 45; (c) Size V Humphrey Field Analyzer printout values of complete loss for a subject age 45. This shows the normative values of the related software for age 45; (d) mean of two tests and interindividual standard deviations for size VI

Figure 4.

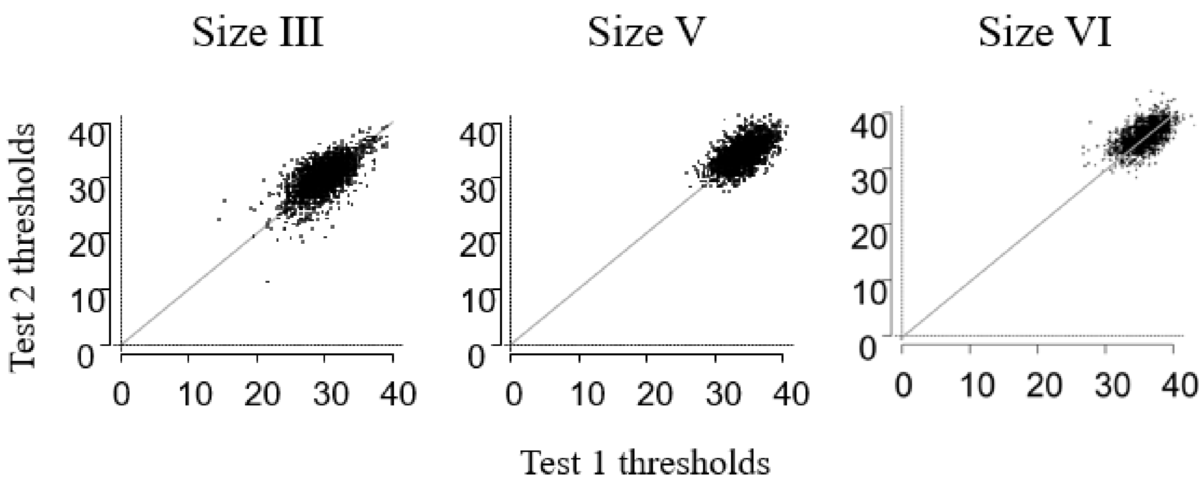

Figure 4. Thresholds of test 1 plotted against test 2 for the different sizes. Note the greater scatter for the size III stimuli reflecting higher variability.

Figure 5.

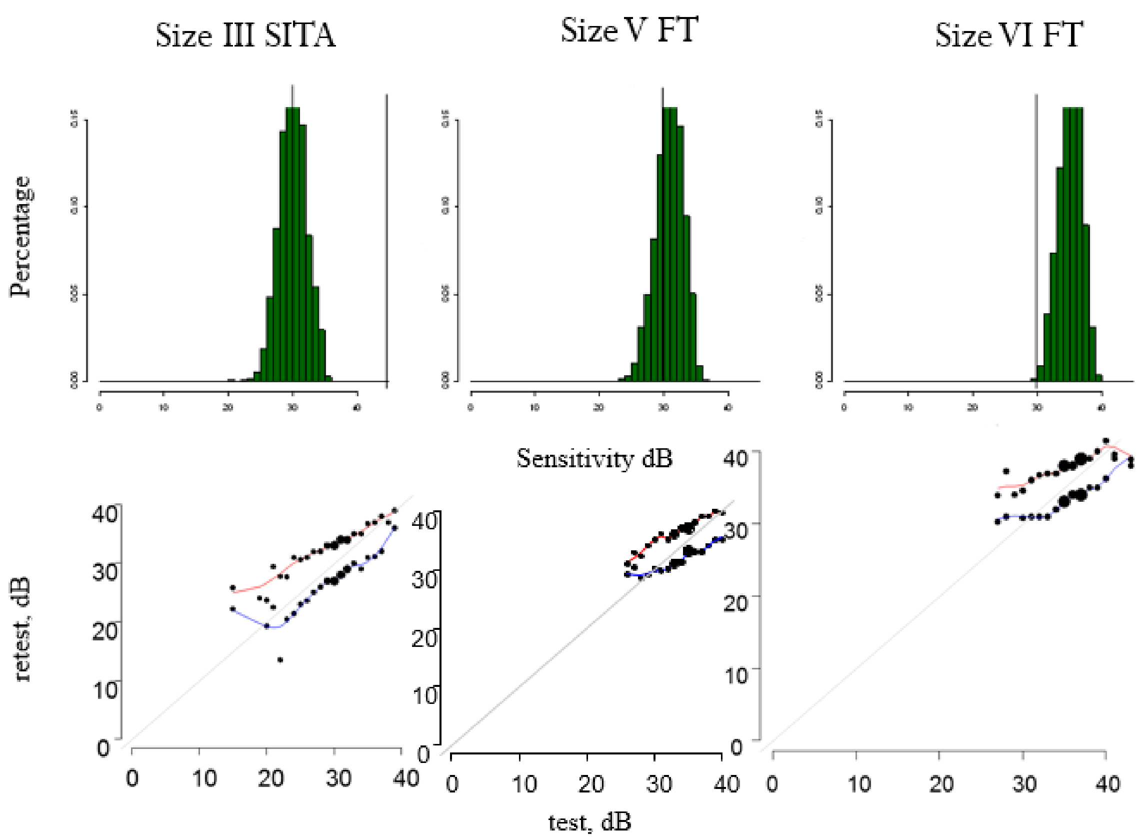

Figure 5. Top row shows the retest variability histograms for the different stimulus sizes. The bottom row shows the 95% confidence interval for the scatttergrams of figure 4.

Examination test times for size III SITA was 4.97 ± 0.66 minutes and for full threshold testing was 9.76 ± 0.80 minutes with Size V and 8.94 ± 0.53 for Size VI testing. The average false positive and false negative rates were all below 4%.

4. Discussion

Standard automated perimetry has two major limitations, a restricted dynamic range, and increasing variability with increasing visual field damage. With regard to the latter, Heijl and colleagues[21, 22] investigated the variability in 51 eyes of 51 experienced glaucoma participants representing all stages of optic nerve damage. The patients, all clinically stable, were tested four times in a four-week period using size III full threshold testing with the HFA. Test locations, initially measured with 6 dB loss, had a 90% prediction interval from -1 to -16 dB. With 8-18 dB loss initially, the 95% prediction interval nearly covered the full measurement range of the instrument (0-40 dB). An important finding of Heijl and coworkers, also observed by others,[23-29] is that pointwise intertest variability increases dramatically with decreasing sensitivity of the test location. A major ramification of this finding is that areas with the most visual loss have the highest variability. Therefore, the most clinically important regions with highest variability are precisely those in which determination of change is most difficult. There are a limited number of strategies to overcome this dilemma. Our data showing better repeatability using the size V (and size VI) stimuli may represent an improvement over size III testing.

It is said that size V stimuli should not be used routinely because this strategy may fail to detect small defects.[30] However, the 10 degree frequency doubling technology stimulus is over 40 times the size of the 1.7 degree size V stimulus in area and the FDT testing is similar in sensitivity to standard automated perimetry using a size III stimulus (0.43°) for glaucoma and other optic neuropathies.[31-33] Also, as noted above, we have compared size III and size V stimuli using empiric probability plots and there is no statistically or clinically significant difference in sensitivity in glaucoma patients.[9-11]

The standard printout used for size V data (Figure 3c) with the HFA, is not based on a database of normals. The values are set to within one dB of size III thresholds. Presently, the HFA does not have a statistical package with probability plots for the size V stimulus. The normative data used by the HFA (Figure 3c) is substantially different from our values corrected for age. Our values for size V are on average 3 dB higher than for size III. In addition, the HFA gray scale is methodologically the same for size III and V; i.e. the same scale is applied. Since size V thresholds are about 4 dB higher than size III, the gray scaling makes it appear size V is less sensitive. To account for this, the gray scale might be adjusted downwards about one gray scale unit. Lastly, size V values are flagged by the HFA software if they are greater than 4 dB of expected. The combination of the normative (expected) values being too low and the lower variability of size V imply that the criteria for identifying a test location as abnormal when using the HFA printout are too conservative. Our retest variability of our results, suggests for normals at least, test locations should be flagged as abnormal if they deviate by 3 or more dB from expected.

Spatial summation is the property of the visual system that relates stimulus size to luminance. In mathmatical terms, $\log L + k \log A = c$ where L is the light threshold, A is the solid angle of the stimulus and k is the summation coefficient (Ricco's law). For partial summation, *k* has a value between 0 and 1. Spatial summation also gradually increases with increasing distance from the fovea in normal participants;[34, 35] this is likely due to the changes in receptive field size and overlap (density) with eccentricity. Goldmann simplified this relationship by establishing "equivalent stimulus values."[36] These values are based on the relationship -- increasing stimulus diameter by a factor of two is approximately equal to increasing luminance by one-half log unit. Since the Goldmann stimulus diameters increase by doubling of the diameters (e.g. 1, 2, 4, 8 mm), and the standard intensities differ by one-half log unit, a $I4_e$ stimulus is similar in stimulus power to $II3_e$, $III2_e$ and $IV1_e$ stimuli.[37] However, as an approximation for the effect of spatial summation for entire field he estimated *k* to be 0.8.

Sloan showed use of this constant to be an oversimplification and it only held under specific circumstances. She showed there was a gradual increase in the capacity for spatial summation with increasing distance from the fovea; at the fovea and at 15° in the nasal field, *k* is less than 0.8.[38] At 30° and 45° it is greater. In addition, she found the relationship is curvilinear, not linear and therefore not a constant.[38] It also lessened with perimetric training.

Dannheim and Drance's findings confirmed those of Sloan and they showed spatial summation did not change with age.[39] In addition, they found, in glaucoma patients, that spatial summation was no more disturbed than differential light sensitivity.[40] This work, by Sloan, Dannheim and Drance, contradicted Dubois-Poulsen's[41] notion of certain types of visual loss being disorders of spatial summation and that in some types of visual loss, reduction in stimulus size is more efficient in detecting early visual field changes than an equivalent reduction in luminance. However, this idea, that larger sized stimuli have poor resolution for detecting the defects of optic neuropathies such as glaucoma, persists with the standardization of perimetry on a size III stimulus. There is no compelling evidence that this stimulus size is optimal for automated static perimetry, and there is a clear need for further exploration of spatial summation properties in normal and diseased visual systems.

While it is stated that resolution is poorer with size V than size III, this has not been proven. Furthermore, Swanson and coworkers[42, 43] compared size III stimuli with large chromatic and achromatic stimuli in 17 patients with glaucoma. Interestingly, the depth of the defect that they measured was similar for all three stimuli and the larger stimuli had lower variability than the smaller size III stimulus. Also, our data using empiric probability plots with size V and size III suggest at least in glaucoma patients, resolution is similar for the two stimulus sizes.

Our data show this effect of spatial summation producing higher sensitivity with sizes V and VI stimuli, compared to size III. Our results are similar to those of Choplin et. al. who compared sizes III - V,[44] and also Sloan who used sizes 0 - V.[38] The higher mean sensitivity is best explained by increased receptive field coverage and resultant spatial summation.[45] This also appears to be the explanation for the findings of Wilensky and coauthors.[7]

Swanson and colleagues[46] investigated the relationship of stimulus size to sensitivity in patients with retinitis pigmentosa and normals. In the normals, they found a size effect of 5.4 dB; they defined size effect as the difference in sensitivities of size III and V. This is similar to our difference of 4.2 dB. They found a much greater size effect in the patients with retinitis pigmentosa. They discuss two types of spatial summation: linear summation and probability summation. The results of normal participants are closer to those predicted by probability summation and the retinitis pigmentosa patients closer to linear summation.[46]

Although variability is less using the size V stimulus and in glaucoma patients it is as sensitive for defect detection as size III, it is unclear whether using this stimulus size will allow earlier detection of change in areas of moderate visual field damage. It is possible that this stimulus may be more resistant to change from visual loss for the same reason (undersampling) it gives a reduction in variability. On the other hand, its lower variability may allow for tighter confidence limits and earlier detection of change.

5. Conclusion

In conclusion, while sensitivities of the larger stimuli are slightly greater foveally, our results indicate the sensitivity is substantially greater for non-foveal test locations. In addition, variability remains low once sensitivity falls below 25 - 30 dB using size V stimuli while it is rising with size III testing. Because of its enhanced dynamic range, size V testing is a logical choice for patients with moderate to advanced glaucoma as stimulus size VI is not available with `the commercial versions of the HFA perimeters. The current statistical analysis package of the HFA for size V could be updated with regard to its normal values. A normative database for size V stimuli would aid practitioners and facilitate investigations so that the optimal stimulus size can be chosen for the appropriate clinical situation.

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