

RELATIONSHIP BETWEEN PERIMETRIC LIGHT SENSITIVITY AND OPTIC DISC NEURORETINAL RIM AREA

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Introduction

The presence of glaucoma is conventionally defined by the presence of a visual field defect; it is the 'gold standard' with which other tests are compared. Since the glaucomatous process is associated with loss of retinal ganglion cells and neuroretinal tissue at the optic disc, the relationship between the functional and structural changes is of great importance in the understanding of the disease process, and in the clinician's interpretation of the state of the disease.

It has been widely reported that, in primary open-angle glaucoma (POAG), visual field loss, as measured by conventional automated perimetry, is preceded by neuroretinal rim loss¹⁻⁴. It is not clear whether this arises because of difficulty in detecting functional damage early in the course of the disease, or because there is a 'functional reserve' in the system, so that functional loss is only recognized once the reserve has been lost. Previous studies have plotted optic disc neuroretinal rim area against differential light sensitivity (DLS), measured in decibels⁵⁻⁸. The plots show a curvilinear relationship, with large changes in neuroretinal rim area and corresponding small changes in decibel values when the rim area is large, and small changes in neuroretinal rim area and corresponding large changes in decibel values when the rim area is small. The conclusions drawn have suggested a changing relationship between structural and functional measures as the disease progresses. However, given the uncertain physiological relationship between DLS and neuroretinal rim area (and retinal ganglion cell numbers), the appearance may simply reflect the logarithmic DLS scale.

Acuity perimetry (high-pass resolution perimetry) has been proposed as a measure of ganglion cell spacing⁹, with a linear relationship between the minimal angle of resolution (MAR) and ganglion cell spacing. The number of ganglion cells (per degree) is the reciprocal of spacing, and is therefore related to the reciprocal of the MAR. When the acuity threshold (MAR) values are plotted on a decibel scale, a linear

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relationship with the DLS decibel thresholds has been found^{10 11}. One would, therefore, expect MAR values and light intensity (apostilbs) to have a linear relationship, and ganglion cell numbers to be related to the reciprocal of light intensity.

The neuroretinal rim area is a measure of ganglion cell axon cross-sectional area, of varying obliquity depending on the course of fibers through the disc, together with other elements, such as supporting glia and blood vessels. The rim area is, as such, a surrogate for ganglion cell numbers, though the exact relationship between the two has not been established. As a measure of cross-sectional area, a linear relationship between rim area and axon numbers would be expected. Similarly, a linear relationship between rim area and the reciprocal of light intensity would be expected.

The purpose of this study was to evaluate the relationship between DLS and neuroretinal rim area, and to compare the conventional decibel scale with a new scale: the reciprocal of light intensity.

Methods

Subjects

Two groups of subjects, normal controls and patients with early glaucomatous field defects, were recruited prospectively as part of a study on the early detection of glaucoma. All subjects gave informed consent to the investigations performed, and each had the following: medical and ocular history, slit-lamp biomicroscopy, tonometry, fundus examination, visual field testing, and imaging with the Heidelberg Retina Tomograph.

Normal subjects

Sixty-nine subjects recruited were friends or spouses of patients attending the Ocular Hypertension Clinic at Moorfields Eye Hospital, hospital staff, or volunteers responding to advertisements on the Hospital notice boards and in a pensioners' magazine. Restriction criteria were: Caucasian ethnic group, ametropia <6 diopters, visual acuity of 20/30 or better, normal visual fields, intraocular pressure of <21 mmHg, no previous ocular history involving the posterior segment, and no family history of glaucoma involving a first degree relative. All subjects performing a normal field test were included irrespective of optic disc appearance. One eye was included in the study, chosen at random if both were eligible.

Glaucoma patients

Thirty-three subjects were taken from the hospital's general glaucoma clinic and from the ocular hypertension clinic. The former were referred to the study on the basis of visual field defect and ocular hypertension only. The latter were patients with ocular hypertension who developed reproducible visual field defects while under review. Restriction criteria were: Caucasian ethnic group, ametropia <6 diopters, visual acuity of 20/30 or better, a visual field defect reproduced on at least three successive occasions, open anterior chamber angle, intraocular pressure >21 mmHg at diagnosis, and no other posterior segment eye disease. One eye was included in the study, chosen at random if both were eligible.

Visual field testing

All visual field testing was performed using the Humphrey Field Analyser 24-2 program. Reliability criteria applied were: fixation losses <30%, false positive responses <15%, and false negative responses <30%.

A normal visual field was taken to be one in which the retinal sensitivity at all locations was better than the eccentricity-related thresholds given in the Advanced Glaucoma Intervention Study (AGIS) protocol¹².

A glaucomatous visual field was taken to be one in which a defect¹² was reproduced on three successive occasions at the same location. Only patients scoring 1-5 (early glaucoma) were included.

Imaging

All subjects were imaged using the Heidelberg Retina Tomograph (HRT) in the 10*10 degree frame. All images were obtained by one of two trained technicians. Imaging was performed at the 1.5 cm imaging head/eye distance recommended in the instruction manual as the subject viewed a distant fixation target. Each patient had three high quality scan series recorded at one sitting. The quality of images was assessed with the aid of the HRT software, and by the experience of the technician. The HRT software is able to correct for small eye movements by aligning consecutive images within a scan series. Scan series with movements occurring within a single image in the series, which caused distortion of the image that could not be corrected, were excluded from the study. The mean topography of the three scan series was used for the analysis (software version 2.01). The contour line of the optic disc edge was drawn by one of the authors (DFGH). The standard reference plane was employed and the following parameters were analyzed: optic disc area, rim area, rim volume, cup shape measure, and retinal nerve fiber layer cross-sectional area. Each parameter was calculated for the whole disc (global) and in the six pre-defined segments: temporal, temporal superior, temporal inferior, nasal, nasal superior and nasal inferior.

In addition, the parameter '% expected rim area' was calculated from the rim area and optic disc area¹³. In a normal population, the neuroretinal rim area has a linear relationship to optic disc area, so that the linear regression line that describes the relationship between the two represents the population mean value for the rim at any given disc area. For an individual optic disc, the measured rim area can be expressed as a percentage of the population mean expected for the size of the optic disc.

The visual field was divided into segments corresponding to the HRT predefined sectors (Figs. 1 and 2), and the mean sensitivity in each segment was used for the analysis. The map of corresponding field test points and disc segments was derived from the nerve fiber layer photographs of 69 glaucomatous eyes. An appropriately scaled visual field grid was overlaid on the nerve fiber layer photographs. Where possible, defects and prominent fiber bundles were traced back to the point of entry to the optic disc, and the point of entry, in degrees from the horizontal meridian on the temporal aspect of the disc, was noted. Points in the visual field grid associated with the defect or prominent bundle were then assigned a degree value according to the point of entry into the disc. The visual field grid was then divided according to the predefined segments given in the HRT software analysis.

The mean DLS for segments in the visual field was expressed in two scales: as

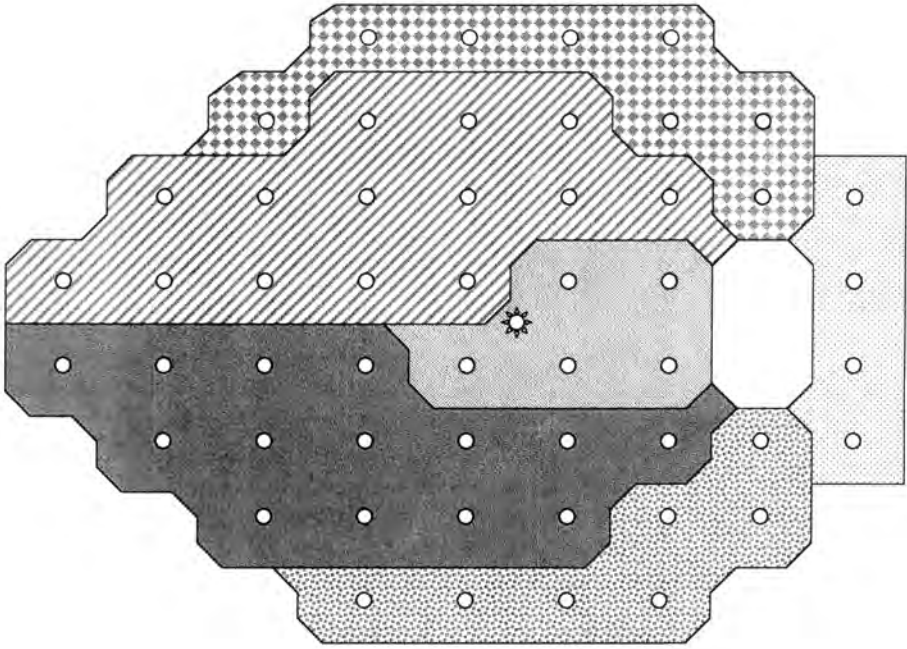


Fig. 1. Visual field segments that correspond to the HRT predefined optic disc sectors.

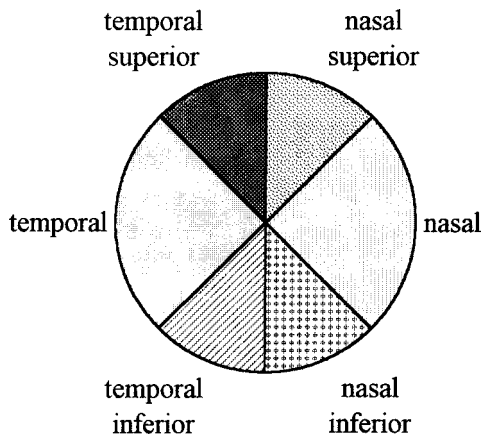


Fig. 2. HRT predefined optic disc sectors.

decibel values and as the reciprocal of the light intensity (1/decamberts). The segmental mean DLS was also calculated as the percentage expected for the age of subject (in 1/decambert scale), using the normal database held in the Humphrey perimeter.

The software SPSS for Windows, version 7.0, and Microsoft Excel 97, were used to perform the statistical analyses. Where linear regression analyses were performed, significance was assumed at $r^2 \geq 0.10$ and $p \leq 0.01$.

Table 1. Study population characteristics

	Normal		Glaucoma	
Age (years)	57.7	sd 12.0	66.5	sd 8.7
Refraction (D)	-0.05	sd 1.97	0.42	sd 1.57
Mean deviation (dB)	0.20	sd 1.00	-3.70	sd 1.69
Mean disc area (mm ²)	1.98	sd 0.35	1.88	sd 0.34
Mean rim area (mm ²)	1.55	sd 0.30	1.00	sd 0.21

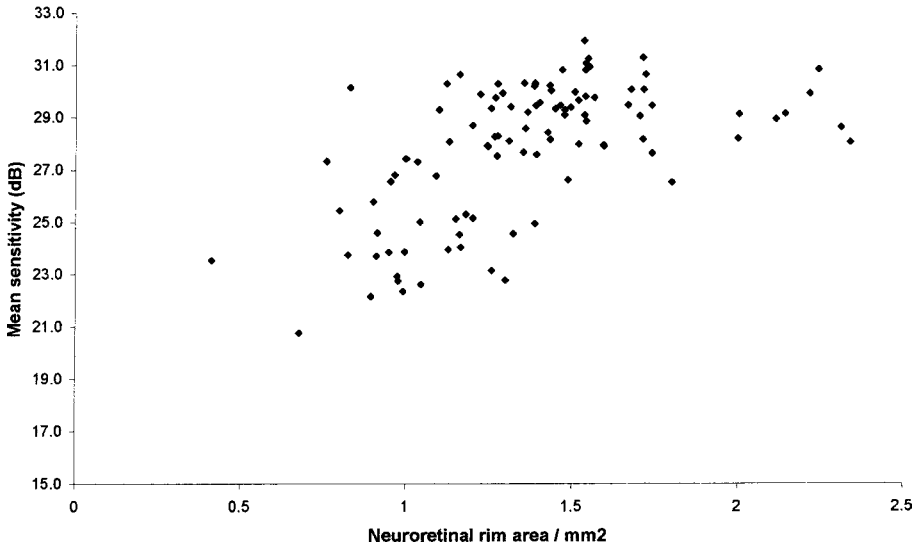


Fig. 3. Scatter plot of DLS in the decibel scale against neuroretinal rim area: whole disc.

Results

The characteristics of the study population are summarized in Table 1.

The relationship between DLS in decibels and neuroretinal rim area is shown graphically for the whole disc in Figure 3, and for the temporal inferior disc sector in Figure 4.

The relationship between DLS in the ‘1/dec Lambert’ scale and neuroretinal rim area is shown graphically for the whole disc in Figure 5, and for the temporal inferior disc segment in Figure 6.

The relationship between the HRT parameters and DLS (1/dec Lambert) appears to be linear. Linear regression analysis was performed between each HRT parameter, for the whole disc and each segment, and DLS (1/dec Lambert). The results are summarized in Table 2. Non-significant values are not displayed.

Linear regression analysis between percentage expected DLS and percentage expected rim area was significant for the whole disc (Fig. 7) and the temporal inferior, temporal superior, and nasal inferior segments, with *r*² values of 0.26, 0.31, 0.23 and 0.16, respectively. At the point representing 52% expected DLS, the percentage expected rim area was: whole disc 52%, temporal inferior sector 38%, temporal superior 42% and nasal inferior 55%.

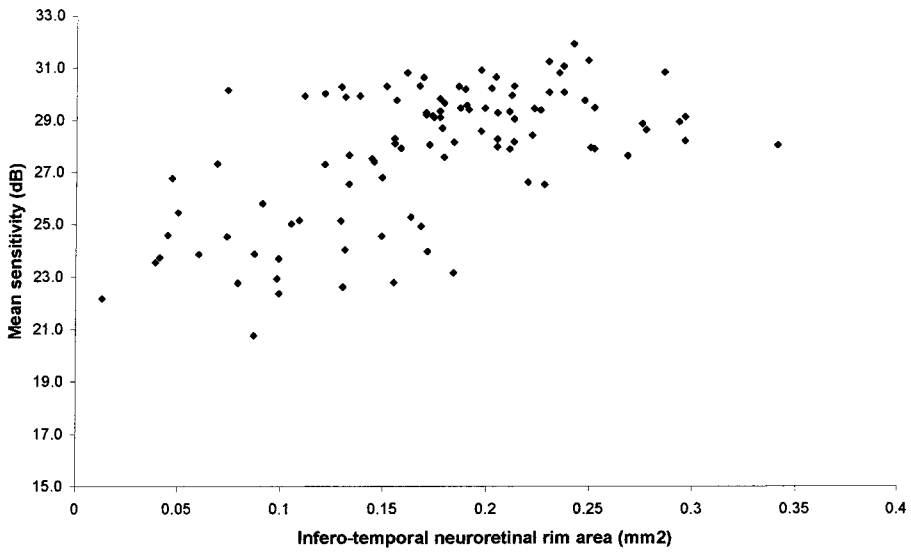


Fig. 4. Scatter plot of DLS in the decibel scale against neuroretinal rim area: temporal inferior disc sector.

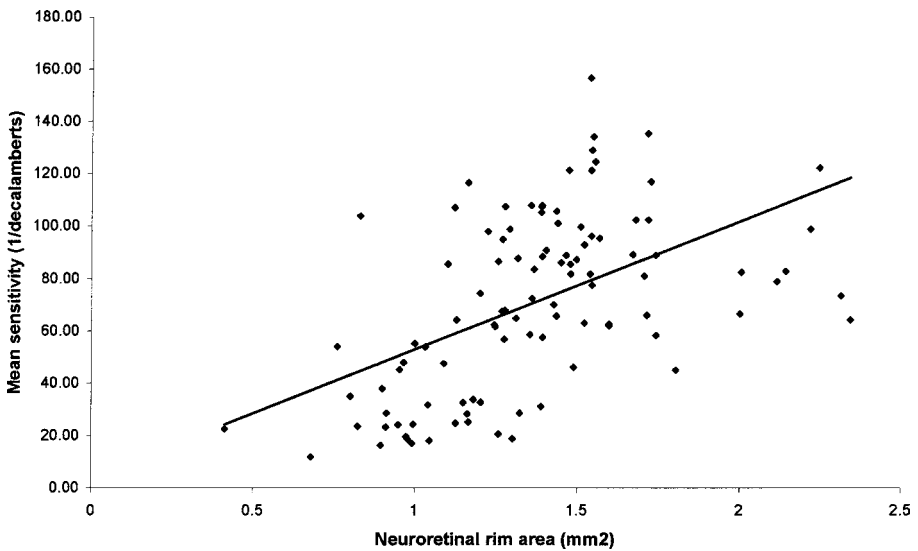


Fig. 5. Scatter plot of DLS in the '1/dec Lambert' scale against neuroretinal rim area: whole disc.

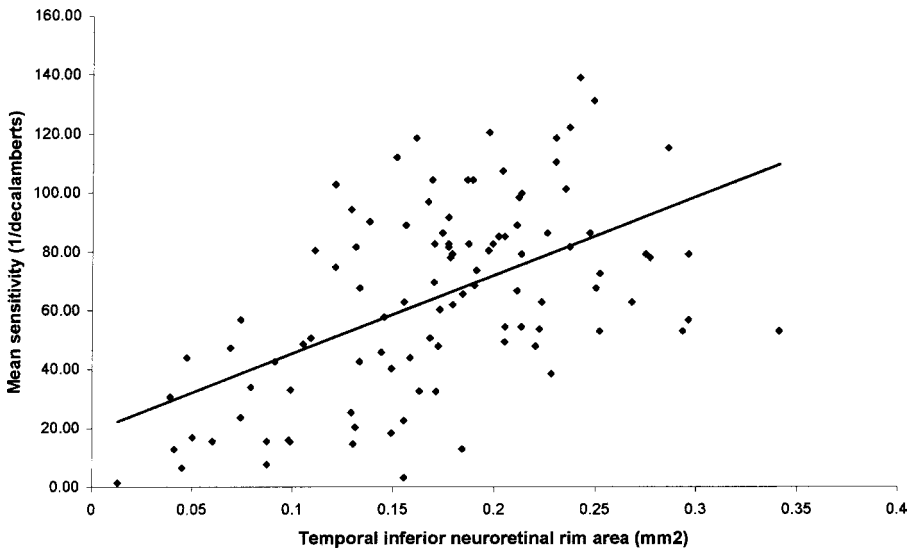


Fig. 6. Scatter plot of DLS in the ‘1/decambert’ scale against neuroretinal rim area: temporal inferior disc sector.

Table 2. R² values for linear regression analyses between DLS and optic disc parameters

	global	TI	Disc sectors		NS	T	N
			TS	NI			
Expected rim area (%)	0.23*	0.35*	0.22*	0.20*	0.10*	0.10#	0.11*
Rim area (mm ²)	0.27*	0.29*	0.25*	0.13*		0.15*	
Rim volume (cmm)	0.25*	0.24*	0.17*	0.18*		0.11*	
RNFL area (mm ²)	0.20*	0.27*		0.18*			
Cup shape measure	0.23*	0.23*	0.13*			0.11*	

Significance levels: #*p*<0.01; **p*<0.001; disc sectors: TI: temporal inferior; TS: temporal superior; NI: nasal inferior; NS: nasal superior; T: temporal; N: nasal

Discussion

The results of the study are consistent with the hypothesis that there is a linear relationship between neuroretinal rim area and the reciprocal of light intensity. This suggests that there is no functional reserve, but a continuous loss of DLS across the range of neuroretinal rim values. The explanation for the observation of structural changes occurring before measurable functional changes lies in the relative variability in the methods of measurement. The normal range (98% prediction intervals) for planimetric neuroretinal rim area has been found to be ±27% to ±40% (depending on the disc segment) around the average value¹³. In other words, rim loss can be detected when between 27% and 40% has been lost. In the visual field, for a central point of mean sensitivity 32.2dB, the inter-individual standard deviation of sensitivities is about 1.9dB¹⁴. The 95% confidence interval will therefore be approximately 3.7dB, giving a lower limit of 28.5dB. 32.2dB represents a light intensity of 6.03 apostilbs, and 28.5dB represents 14.13 apostilbs. In other words, the lower limit of

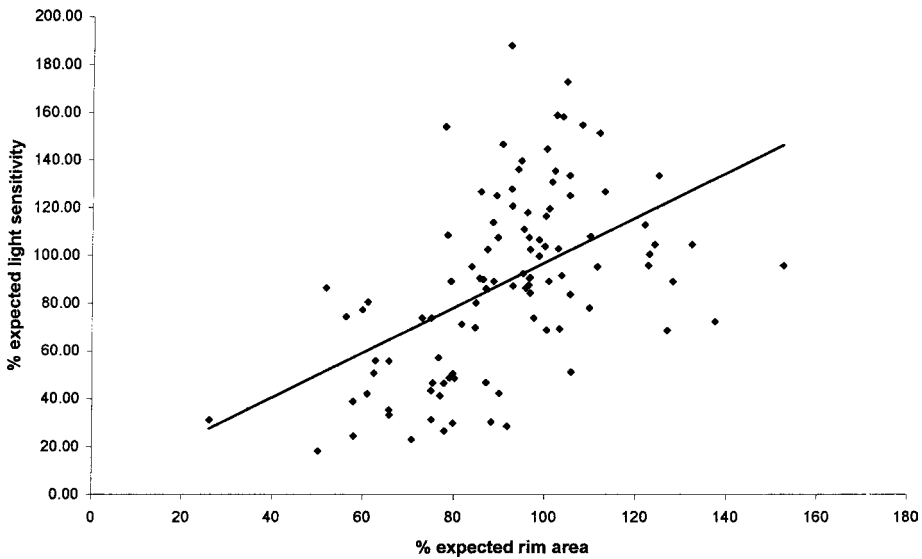


Fig. 7. Scatter plot of percentage expected DLS (in the '1/dec Lambert' scale) against percentage expected rim area: whole disc.

normal variability represents a light intensity a little over doubled (or DLS over halved in the scale used in this study) before a point can be identified as abnormal. Furthermore, a cluster of points is usually required before a whole field is identified as abnormal. On this basis, even if changes occur equally in the neuroretinal rim and visual field in early glaucoma, the structural changes will be apparent first. Newer testing algorithms, such as the SITA¹⁵, may improve the ability to detect abnormal points in the field by reducing variability.

A stronger relationship between the DLS and neuroretinal rim area was apparent in some parts of the neuroretinal rim than in others. The probable explanation for this is that there is a greater number of visual field test points in some field segments than others (Fig. 1). As a result, there is greater sampling, and noise is averaged out. The temporal and nasal sectors occupy the largest extent of the optic disc (each 90°), and have fewest corresponding field test points, resulting in poorer precision.

The relationship between sensitivity loss and neuroretinal rim loss found in this study suggests that a 50% loss of neuroretinal tissue corresponds to a 50% loss in DLS in the 1/dec Lambert scale. A 50% loss is equivalent to 3dB. For a further 50% loss of neuroretinal tissue, from this reduced level, another 3dB reduction in sensitivity would be expected. On the basis of a histological study, Quigley *et al.* estimated a 20% reduction in ganglion cell numbers for a 5dB loss in DLS for peripheral test points, and a 50% reduction for a 5dB loss for central test points¹⁶. However, linear regression analysis was performed with all test points over the entire range of DLS in the decibel scale. The relationship may have appeared different had ganglion cell numbers been plotted against DLS on the 1/dec Lambert scale. A recent monkey study¹⁷ demonstrated a curvilinear relationship between percentage ganglion cell loss, measured histologically, and DLS loss measured in decibels. It would be interesting to see if the logarithmic (decibel) DLS scale can account for this non-linear relationship.

The study presented here takes no account of possible differences in the relationship between DLS and neuroretinal rim area that relate to the eccentricity of the visual field test points (and, therefore, ganglion cell density). It is intended that future studies will address this issue.

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