Relationship between Electrophysiological, Psychophysical, and Anatomical Measurements in Glaucoma

David F. Garway-Heath,1 Graham E. Holder,2 Fred W. Fitzke,3 and Roger A. Hitchings1

PURPOSE. To evaluate the relationship between electrophysiological, psychophysical, and structural measurements in normal and glaucomatous eyes and to test the hypothesis that there is a continuous structure–function relationship between ganglion cell numbers and visual field sensitivity.

METHODS. Thirty-four normal subjects and 40 patients with glaucoma were examined with the pattern electroretinogram (PERG), perimetry and retinal tomography. Transient and steady state (SS) PERGs were recorded, and peak (P)-to-trough (N) amplitude was measured. The unit of differential light sensitivity (DLS) in perimetry is the decibel. The decibel is 10 \times \log(1/Lambert), where the Lambert is the unit of test spot intensity. PERG amplitudes were correlated with decibel and 1/Lambert DLS for the central 18° of the visual field and with neuroretinal rim area in the temporal part of the optic disc. Age-related changes in the structural and functional measurements were sought. The correlation between variables was investigated by linear and quadratic regression analysis. A quadratic \( (P = ax^2 + bx + c) \) fit was taken to be significantly better than a linear fit if the coefficient \( b \) for the \( x^2 \) term was significant at \( P < 0.05 \).

RESULTS. A quadratic fit between decibel DLS and PERG amplitude (transient PERG: \( R^2 = 0.40, P = 0.0000 \); SS PERG: \( R^2 = 0.52, P = 0.0000 \)) was significantly better than a linear fit. There was a linear correlation between 1/Lambert DLS and PERG amplitude (transient PERG: \( R^2 = 0.44, P = 0.0000 \); SS PERG: \( R^2 = 0.39, P = 0.0000 \)). There was a linear correlation between temporal neuroretinal rim area and PERG amplitude (transient PERG: \( R^2 = 0.17, P = 0.0003 \); SS PERG: \( R^2 = 0.20, P = 0.0001 \)). A quadratic fit between decibel DLS and temporal neuroretinal rim area (\( R^2 = 0.38, P = 0.0000 \)) was significantly better than a linear fit. There was a linear correlation between 1/Lambert DLS and temporal neuroretinal rim area (\( R^2 = 0.30, P = 0.0000 \)). Both DLS and PERG amplitude declined with age in the normal subjects. The rate of decline was \(-0.17\%\), \(-0.74\%\), \(-0.75\%\), and \(-0.78\%\) per year for decibel DLS, 1/Lambert DLS, transient PERG, and SS PERG, respectively.

CONCLUSIONS. There is a curvilinear relationship between decibel DLS and both PERG amplitude and neuroretinal rim area, and a linear relationship between 1/Lambert DLS and PERG amplitude and neuroretinal rim area. These findings support the hypothesis that there is no ganglion cell functional reserve but a continuous structure–function relationship, and that the impression of a functional reserve results from the logarithmic (decibel) scaling of the visual field. (Invest Ophthalmol Vis Sci. 2002;43:2213–2220)

The relationship between functional and anatomical measurements in primary open-angle glaucoma (POAG) is of fundamental importance to our ability to infer the extent of glaucomatous damage and to estimate rates of disease progression from such measurements. The extent of visual field loss is commonly used to estimate the severity of POAG, and scoring systems have been developed both to stage and describe progression of POAG.1,2 Several studies suggest that visual field loss is preceded by neuroretinal rim loss3–6 and that progression of disc change may be detected before that of visual field change.7 However, the precise nature of the relationship between visual field loss and anatomical measurements is poorly understood.

Visual function, as measured by white-on-white perimetry, is typically recorded in the logarithmic decibel (dB) scale. In considering the relationship between functional and structural measurements, there is evidence that the relationship between decibel light sensitivity and ganglion cell number is curvilinear8–9 and that the curvilinear relationship may be explained at least in part by the logarithmic scale.9 Ganglion cell axon number correlates with the neuroretinal rim area,10 and a curvilinear relationship has also been reported between decibel visual field sensitivity and neuroretinal rim measurements.11–14 Large changes in neuroretinal rim area and corresponding small changes in decibel values are seen when the rim area is large, and small changes in neuroretinal rim area and corresponding large changes in decibel values are seen when the rim area is small. The logarithmic scale accentuates sensitivity changes in the visual field at low-decibel levels and minimizes changes at high-decibel levels. Thus visual function changes are less apparent in the early stages of structural damage, giving the impression that structural changes occur first.

The pattern electroretinogram (PERG) is believed to reflect function in the inner retina15,16 and represents a massed ganglion cell response to a suprathreshold stimulus.16 PERG amplitudes should be related to the number of functioning ganglion cells in the retina. Amplitudes have been reported to be reduced in glaucomatous eyes,19–25 and a correlation of PERG amplitude with visual field sensitivity22,26–28 and optic disc structure22,29 and retinal nerve fiber layer thickness30,31 has been reported. The previous literature on the PERG and glaucoma has recently been reviewed.32

The purpose of this study was to evaluate the relationship between differential light sensitivity (DLS), PERG amplitudes, and neuroretinal rim area in normal and glaucomatous eyes and to test the hypothesis that there is a continuous structure–function relationship between ganglion cell number and visual field sensitivity.
METHODS

Normal control subjects 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, and the study conformed to the tenets of the Declaration of Helsinki. Each had the following examinations: medical and ocular history, tonometry, slit-lamp biomicroscopy, PERG, visual field testing, and imaging by retinal tomography.

Normal Subjects

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 bulletin boards and in a pensioners’ magazine. Restriction criteria were white ethnic group, ametropia less than 6 D, visual acuity of 20/30 or better, normal visual fields, intraocular pressure of less than 21 mm Hg, no previous ocular history involving the posterior segment, and no family history of glaucoma in a first-degree relative. All subjects with normal field test results were included, regardless of optic disc appearance. One eye was included in the study, chosen at random if both were eligible. Thirty-four subjects satisfied the criteria for the study.

Patients with Glaucoma

Subjects were taken from the hospital’s general glaucoma clinic (n = 33) and from the ocular hypertension clinic (n = 7). The former were referred to the study on the basis of visual field defect and history of ocular hypertension only. The latter were patients with ocular hypertension in whom reproducible visual field defects developed while they were under review. Restriction criteria were white ethnic group, ametropia less than 6 D, visual acuity of 20/30 or better, a reproducible visual field defect, open anterior chamber angle, intraocular pressure more than 21 mm Hg at diagnosis, no miotic therapy, and no other posterior segment eye disease. Intraocular pressures were controlled by topical ß-blocker medication only, or after surgery. All subjects with a reproducible visual field defect and a history of ocular hypertension were included, regardless of optic disc appearance. One eye was included in the study, chosen at random if both were eligible. Forty subjects satisfied the criteria for the study.

Pattern Electroretinogram

The pattern electroretinogram (PERG) was recorded with gold foil corneal electrodes and a reference electrode on the skin near the lateral canthus. The checkerboard stimulus subtends 16° by 22° on the retina and comprises checks of between 95% and 98% contrast, with each check subtending 0.5° (Fig. 1). Transient responses were recorded at a pattern-reversal rate of 3 Hz and steady state (SS) responses at a pattern reversal rate of 8 Hz. Approximately 250 sweeps were averaged for each response, and at least four responses were recorded for each eye. PERG test results were reported by a consultant electrophysiologist (GH) who was masked to the subject diagnosis. Because of the inherent difficulty in accurately establishing a baseline, the magnitude of the transient response was measured from the peak (P) of the P50 component to the trough (N) of the N95 component, as recommended by the International Society for Clinical Electrophysiology of Vision.

Visual Field Testing

All visual field testing was performed using the Humphrey Field Analyzer’s (model 640 with StatPac-2; Zeiss-Humphrey Systems, Dublin, CA) 24-2 full threshold strategy, with the Goldmann size III target. Near refractive correction was used, calculated according to the subjects’ age by the perimeter software. Reliability criteria applied were fixation losses less than 30%, false-positive responses less than 15%, and false-negative responses less than 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) protocol. A glaucomatous visual field was taken to be one in which a defect scoring 1 or more in the AGIS protocol was reproduced on three successive occasions at the same location.

Imaging

All subjects were imaged by tomography (Heidelberg Retina Tomograph [HRT]; Heidelberg Engineering GmbH, Heidelberg, Germany) in the 10° × 10° 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 mean topography of the three–scan series was used for the analysis (HRT software version 2.01). Images with a mean SD of height measures of more than 50 μm were excluded from further analysis. The contour line of the optic disc edge was drawn by one of the authors (DFGH). The standard reference plane was used.

Recruitment was restricted to the white ethnic group, because it is known that optic disc morphology can vary between different ethnic groups. Visual field and PERG tests and HRT imaging were performed within 4 months of each other in all subjects.

Data Analysis and Statistics

The DLS at the central 16 test points (18° × 18°) corresponds to the area tested in the PERG (Fig. 2). The decibel is 10 log (1/Lambert). Mean DLS was calculated for the central 16 points in the decibel and the 1/Lambert scales.

The relationship between visual field locations and regions of the optic disc has been described previously. The temporal half of the optic disc receives ganglion cell axons from the central 16 test points of the visual field and the area tested in the PERG (Fig. 3). Neuroretinal rim area was recorded for the temporal three of the six predefined segments given in the HRT analysis. Parameter differences between groups were assessed with a two-tailed t-test assuming unequal variance.

The following correlations were assessed in the combined normal–glaucoma group: PERG amplitude and central visual field sensitivity, PERG amplitude and temporal neuroretinal rim area, and central visual field sensitivity and temporal neuroretinal rim area. In addition, the relationship between age and PERG amplitude, central visual field sensitivity, and temporal neuroretinal rim area was investigated in the normal group.
Correlations between measurements were sought by linear or quadratic regression analysis. A quadratic ($y = ax + bx^2 + c$) fit was taken to be significantly better than a linear fit if the coefficient ($b$) for the $x^2$ term was significant at $P < 0.05$. Statistical significance was assumed at $P \leq 0.05$ for all analyses.

Statistical analyses were performed on computer (SPSS for Windows, ver.10.0; SPSS Science, Chicago, IL; Excel 97 SR-2; Microsoft, Redmond, WA).

RESULTS

The study population characteristics are summarized in Table 1. There was a range in severity of visual field loss in the glaucoma group. Thirty subjects had a mean deviation (MD) of more than $-5$ dB, seven had an MD of between $-5$ and $-10$ dB, and three had an MD of between $-10$ and $-15$ dB.

The transient and SS PERGs, central visual field mean DLS in decibels and 1/Lambert, and the HRT temporal neuroretinal rim areas are shown in Table 2. All parameter values were significantly lower in the glaucoma group.

PERG amplitudes ($R^2 = 0.15$, $P < 0.02$ for the transient and $R^2 = 0.25$, $P < 0.002$ for the SS) and both decibel and 1/Lambert visual field central mean DLS (both $R^2 = 0.32$, $P < 0.0005$) correlated significantly with age in the normal group. The rates of change were $-0.75\%$, $-0.78\%$, $-0.17\%$, and $-0.74\%$ per year for the transient PERG response, the SS PERG response, decibel mean sensitivity and 1/Lambert mean sensitivity, respectively. Temporal neuroretinal rim area did not correlate with age.

There was a significant correlation between central visual field mean DLS and PERG amplitude in the combined normal-glaucoma groups. A quadratic fit was significantly better than a linear fit for regression of PERG amplitude on decibel DLS: transient PERG $R^2 = 0.40$, $P < 0.0000$ (Fig. 4) and SS $R^2 = 0.32$, $P < 0.0000$. A linear fit was significantly better than a quadratic fit for regression of PERG amplitude on 1/Lambert DLS: transient PERG $R^2 = 0.44$, $P < 0.0000$ (Fig. 5) and SS $R^2 = 0.35$, $P < 0.0000$. A 50% reduction in 1/Lambert DLS (equivalent to 3 dB) was associated with a 36% reduction in transient and SS PERG amplitude. These analyses were also significant when the normal and glaucoma groups were taken separately.

When the data from normal eyes were entered into a multiple linear regression analysis, with age and transient PERG as independent variables and 1/Lambert DLS as the dependent variable, the significance of the coefficient for the age term was $P < 0.005$ and for the PERG term was $P > 0.05$. In a similar analysis of the combined group of normal and glaucomatous eyes the significance of the coefficient for the age term was $P < 0.001$ and for the PERG term was $P < 0.001$.

There was significant correlation between temporal neuroretinal rim area and central visual field mean DLS. Quadratic regression gave the best fit for the correlation of neuroretinal rim area with decibel values ($R^2 = 0.38$, $P < 0.0000$, Fig. 6), and linear regression gave the best fit for the correlation of rim area with 1/Lambert values ($R^2 = 0.30$, $P < 0.0000$, Fig. 7). These analyses were not significant when the normal and glaucoma groups were taken separately. A 50% reduction in 1/Lambert DLS (equivalent to 3 dB) was associated with a 32% reduction in temporal neuroretinal rim area.

There was significant correlation between temporal neuroretinal rim area PERG amplitudes. Linear regression gave the best fit for the correlation of rim area with the transient ($R^2 = 0.17$, $P < 0.0003$, Fig. 8) and SS ($R^2 = 0.20$, $P < 0.0001$) PERG

TABLE 1. Study Population Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects ($n = 34$)</th>
<th>Glaucoma Patients ($n = 40$)</th>
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<tbody>
<tr>
<td>Age (y)</td>
<td>58 ± 11</td>
<td>68 ± 9</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>41</td>
<td>63</td>
</tr>
<tr>
<td>Eye side (% right)</td>
<td>41</td>
<td>43</td>
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<tr>
<td>Visual field MD (dB)</td>
<td>−0.09 ± 1.36</td>
<td>−4.15 ± 3.05</td>
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FIGURE 2. The position of the perimeter’s 24-2 stimulus pattern overlaid on a fundus photograph. The stimulus size is 0.43°. The stimulus spacing and size are to scale. The box encloses the points included in the analyses to compare with PERG amplitudes and neuroretinal rim areas.

FIGURE 3. The relationship between the central visual field and optic disc, derived from a published optic disc–visual field map.36
DISCUSSION

When assessing a patient with glaucoma, it is essential to estimate the amount of glaucomatous damage to set appropriate treatment targets. The amount of glaucomatous damage is usually estimated from the magnitude of visual field loss and extent of neuroretinal rim loss in the optic disc. It is important to understand how field and rim loss are related to each other to identify correctly the stage of disease. Similarly, when assessing the rate of glaucomatous progression, it is important to know whether the relationship between the amount of ganglion cell loss and the measurement of visual function is linear. If there is a curvilinear correlation of decibel DLS with ganglion cell number, then linear models of decibel DLS progression underestimate the rate of change when decibel DLS is near normal and overestimate the rate of progression when field loss is already moderately advanced. The results of this study confirm previous reports of a curvilinear relationship between neuroretinal rim area and decibel visual field loss (Fig. 6),11,12,14 and support the suggestion that the DLS scale of 1/Lambert (Fig. 7) is a more appropriate scale when comparing structural and functional measurements.9 This suggestion is reinforced further by the curvilinear relationship between PERG amplitude and decibel DLS (Fig. 4) and the linear relationship between PERG amplitude and 1/Lambert DLS (Fig. 5) and temporal neuroretinal rim area (Fig. 8).

Previous studies have reported a correlation of PERG amplitude and visual field sensitivity,22,26,28 and one study has demonstrated hemifield PERG–DLS correlations.27 Bach et al.28 and Korth et al.,22 in studies using similar methodology, found that in patients with glaucoma, the PERG is often abnormal, even when there are no defects in the central visual field. This finding is supported by the results of our study, which demonstrated large changes in PERG amplitude and corresponding small changes in decibel DLS when the central mean sensitivity was near normal (Fig. 4). However, the linear relationships between 1/Lambert DLS, PERG amplitude, and neuroretinal rim area suggest that there is no functional reserve in the visual system that has to be lost before glaucomatous optic nerve damage manifests. Instead, it suggests that there is a continuous, linear, structure–function relationship, with the number of ganglion cells linearly related to 1/Lambert DLS.9 The impression of a functional reserve is given by the logarithmic nature of the decibel DLS scale. In addition, in the individual patient, because of the high test–retest variability and the nonspecificity of diffuse sensitivity loss in the visual field, structural damage at the optic disc is frequently identified before reproducible visual field defects. This adds to the impression of a functional reserve.

Although the PERG and perimetry both test aspects of visual function, they differ in their nature. The PERG is an objective measure of massed ganglion cell responses to a suprathreshold stimulus, whereas perimetry depends on subjective responses to a threshold stimulus.

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects</th>
<th>Glaucoma Patients</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient PERG (µV)</td>
<td>4.08 ± 1.28</td>
<td>2.78 ± 1.07</td>
<td>&lt;0.0000</td>
</tr>
<tr>
<td>Steady state PERG (µV)</td>
<td>2.77 ± 0.87</td>
<td>1.96 ± 0.89</td>
<td>0.0003</td>
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<tr>
<td>Central mean DLS (dB)</td>
<td>31.1 ± 1.1</td>
<td>26.5 ± 3.5</td>
<td>&lt;0.0000</td>
</tr>
<tr>
<td>Central mean DLS (1/Lambert)</td>
<td>1403 ± 347</td>
<td>728 ± 287</td>
<td>&lt;0.0000</td>
</tr>
<tr>
<td>Temporal neuroretinal rim area (mm²)</td>
<td>0.64 ± 0.14</td>
<td>0.36 ± 0.13</td>
<td>&lt;0.0000</td>
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</table>
Both the PERG amplitude and the perimetric response threshold might be expected to be determined by the relationship of stimulus area to ganglion cell density. The stimulus areas are similar in both tests: The PERG stimulus was a 0.5° square within a regular checkerboard and the perimetric stimulus measured 0.43°. Neither test used stimuli scaled to account for changes in ganglion cell density with eccentricity. Thus, spatial summation effects are not accounted for in either test. These similarities between the tests probably account for the striking correlation between PERG amplitude and 1/Lambert DLS in this study (Fig. 5).

PERG amplitude was less strongly related to temporal neuroretinal rim area than to DLS. This is in agreement with a previous study, although the correlation in this study, using the HRT to quantify neuroretinal rim area, was slightly better than that in the previous report in which planimetry was used. It is not surprising that the PERG amplitude and DLS correlated well, because they both measure related aspects of visual function. The neuroretinal rim area is a surrogate for, not a direct measurement of, ganglion cell number. It 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 measured rim area may be affected by the slope of the rim–cup edge and positioning of the reference plane by the retinal tomograph’s software. Because axon size is related to ganglion cell eccentricity and axons from near the fovea enter the disc at its temporal side, the relationship between ganglion cell number and neuroretinal rim area may change around the circumference of the disc. These factors may explain the rela-

**FIGURE 5.** Plot of central visual field mean sensitivity in 1/Lambert against transient PERG (N+P) amplitude.

**FIGURE 6.** Plot of central visual field mean sensitivity in decibels against temporal neuroretinal rim area.
tively poor correlation between the measurements of structure and function.

Visual function declined with increasing subject age, and this largely, although not completely, explained the relationship between DLS and PERG amplitude in the normal group. However, the relationship between DLS and PERG amplitude in the combined normal-glaucoma group cannot be explained by age-related changes in visual function alone, because the relationship remained significant when age was introduced into the regression model. The age-related rate of decline in decibel DLS in this study is almost identical with that reported by Heijl et al.

It is important to consider possible confounding factors in the study. Most of the patients with glaucoma were taken from the general glaucoma clinic and, although concordance of optic disc and visual field change was not a requirement for entry into the study, the diagnosis of glaucoma often requires such concordance. However, all patients had ocular hypertension at diagnosis and had reproducible visual field defects, and it is not thought that patients with these features would be excluded from the clinic if nonconcordant optic disc change were present. If this bias is present, it may affect strength of the
optic disc–visual function relationship, but probably not the linear–curvilinear pattern. 

Lens opacity and age-related miosis may account for some of the correlation between the visual field and PERG results, even though a visual acuity of better than 20/40 was required in all subjects. However, the age-related decline in ganglion cell numbers, estimated at approximately 0.36% to 0.62% per year in cross-sectional histologic studies and imagining studies, may account for most of the 0.75% per year loss of DLS and PERG amplitude. Other factors may play a role in the age-related DLS and PERG amplitude reduction. Senile miosis has been implicated, although this cannot explain the age-related change in some protocols. Subject age, which may be viewed as a surrogate measure of changes such as unquantified lens opacity, miosis, and age-related ganglion cell loss, accounts for most of the relationship between DLS and PERG amplitude in the normal subjects. This was not the case in the combined normal and glaucoma group, in which glaucoma-related ganglion cell loss was presumably an important factor. The likely effect of the age-related factors is to increase the strength of the DLS–PERG relationship but not the linear–curvilinear pattern.

In summary, the findings in this study of a linear relationship between PERG amplitude, 1/Lambert DLS and neuroretinal rim area support the hypothesis that there is no ganglion cell functional reserve, but a continuous structure–function relationship.

References


