Comparison of Psychophysical and Electrophysiological Testing in Early Glaucoma

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Purpose. To compare the sensitivity and specificity of a wide range of psychophysical and electrophysiological tests in the detection of early glaucomatous damage.

Methods. Forty-three normals and 43 patients with early glaucoma, some still without field defects, were tested with differential light threshold perimetry, short-wavelength automated perimetry, high-pass resolution perimetry, motion detection, flicker contrast sensitivity, flickering and isoluminantly matched letter tests, and pattern and flash electroretinography, including photopic, scotopic, oscillatory potentials, and 30 Hz flicker. Receiver operating characteristic analysis was applied to continuous variables derived from each of the tests.

Results. Most parameters reflected glaucomatous loss to some degree, even though only single variables were analyzed separately in the receiver operating characteristic analysis. The pattern electroretinogram and some of the letter acuity tests had the best sensitivity and specificity, followed by short-wavelength automated perimetry and high-pass resolution perimetry. Motion detection, flicker contrast, and flash electroretinogram parameters scored poorly. Six patients with normal results on the Humphrey field test had abnormal results on many of the other tests.

Conclusions. Applying different psychophysical and electrophysiological tests may add to our ability to detect early glaucomatous damage. Invest Ophthalmol Vis Sci. 1996;37:2651–2662.

The detection of glaucoma in its earliest stages is a major goal for clinicians and researchers. Standard white-on-white static threshold perimetry using such automated systems as the Humphrey Field Analyzer (Humphrey Instruments, San Leandro, CA) and the Octopus perimeter (Interzeag, Schlieren, Switzerland) has helped in the early recognition of field loss and in its quantification for accurate follow-up and assessment of progression of the disease. There are many other psychophysical techniques available for detecting damage to the visual system. There is also interest in the objective information provided by the pattern electroretinogram (PERG). In this study, various tests were performed on patients with early glaucoma and on normal controls. Results were compared to determine the sensitivity and specificity of the test parameters for use in the diagnosis of early glaucoma.

Short-wavelength automated perimetry (SWAP) uses a blue stimulus on a bright yellow background to isolate the blue cone pathway. In recent years, it has been reported as a superior technique for detecting early glaucomatous field loss. Scotomas were deeper and larger than they were on conventional perimetry.[1–6] High-pass resolution perimetry (HRP), or ring perimetry as described by Frisén,[7–9] is now a well-established alternative form of perimetric testing for screening and for follow up of glaucomatous visual field loss.[10–16] Its advantages over conventional automated static threshold perimetry are reduced testing time, greater patient acceptance,[17] low intratest and intertest variability,[18,19] and a minimal learning curve.[20] It is thought to reflect predominantly the parvocellular (P cell) pathway.[21]

Motion detection, which has been described as

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abnormal in patients with ocular hypertension and in those with early glaucoma,[22-24] is considered a predominantly magnocellular (M cell) function.[25] Many studies have described abnormalities in both spatial contrast sensitivity and temporal flicker contrast sensitivity in glaucoma.[26,27] We used a series of tests that measured motion coherence thresholds and then presented flickering gratings for contrast sensitivity. Static and flickering letter tests also were designed to target specifically the M cell pathway, which is thought to be specialized for temporal resolution and the detection of low-contrast, achromatic stimuli.[22] An isoluminantly matched letter test also was designed and used to target P cell channels, which are sensitive to color vision and spatial frequencies at high contrast.

The pattern ERG is an electrical potential thought to be derived from retinal ganglion cells and neighboring inner retinal structures.[28,29] It has been shown to be abnormal in patients with established glaucoma,[10,30-35] and it has been investigated in the diagnosis of patients with suspected or early glaucoma.[10,33-37] In contrast to the the PERG, the flash ERG in glaucoma has been less conclusive. It has been reported to be abnormal in advanced glaucoma,[38,39] but more recent reports have shown changes in earlier cases.[35,40-42] Oscillatory potentials (OPs) have been reported to be reduced in several studies.[35,43,44]

This study compares all the above tests in a group of normals and in patients with early glaucoma. Continuous parameters derived from the tests were analyzed using receiver operating characteristics (ROC). We also analyzed the optimal cut-off points for sensitivity and specificity.

METHODS

Two groups of persons, one consisting of 43 normals (mean age, 56.8 ± 12.2 years) and one consisting of 43 patients with glaucoma (mean age, 60.2 ± 11.0 years) ($P > 0.17$), were tested with a full range of psychophysical and electrophysiological tests. The psychophysical tests were performed on one eye of each person during one visit in random sequence, with rest periods between tests. The tests were Octopus 123 (G-1 program), SWAP (using a 30-2 stimulus pattern), HRP, motion coherence threshold, flicker contrast sensitivity, and a static, flickering, and isoluminantly matched letter acuity test. On a second visit, a pattern ERG and flash ERGs (photopic, scotopic, oscillatory potentials, and 30 Hz flicker) were recorded. The investigation followed the tenets of the Declaration of Helsinki, and informed consent was obtained from all participants.

Inclusion criteria were corrected visual acuity of ≥6/7.5 and pupils measuring ≥3 mm without dilation. Patients who had undergone intraocular surgery or who had diabetes or other ocular disorders were excluded. The eye to be tested was selected on the basis of lesser field defect or better visual acuity; if there was no clear difference between the eyes, it was chosen randomly. Patients with glaucoma underwent Humphrey 30-2 field testing on multiple occasions before the study and had to have a mean defect (MD) < 12 dB. The MD range was +1.19 to −11.57 dB (mean, −4.04 ± 3.3 dB). In normals, a Humphrey 120-point, three-zone threshold-related screening test was carried out to confirm a normal visual field before further testing was conducted.

The diagnosis of primary open-angle glaucoma required at least two of the following three parameters: confirmed visual field defect on Humphrey 30-2 (defined below), glaucomatous optic disc as judged by stereo disc photography, and intraocular pressure > 21 mm Hg on at least three occasions with the applanation tonometer. The definition of a localized scotoma used the pattern deviation plot on the Humphrey 30-2 program. A minimum scotoma required at least three adjacent points depressed by at least 5 dB on the pattern deviation, with one of the points depressed at least 10 dB or two adjacent points depressed by 10 dB. Along the horizontal meridian, three adjacent points depressed by 5 dB qualified as a scotoma. The cluster of abnormal points that included the 10 dB nucleus could not cross the horizontal meridian. Points immediately above and below the blind spot were excluded. Rim points—except for the two nasal horizontal rim points—were not included in the definition of the scotoma. Masked grading of stereo disc photographs was performed by three observers, who had to reach a consensus on whether the disc was normal, suspect, or definitely glaucomatous. Patients with suspect discs were not included in this study.

With this classification system, six patients had elevated pressures with glaucomatous discs but still had normal fields. These patients were included in the group with glaucoma. Thirty patients had primary open-angle glaucoma with a history of elevated intraocular pressure, and 13 had normal tension glaucoma. None of the patients in the study had a combination of elevated pressure and abnormal fields with normal discs.

In normals, intraocular pressure was <21 mm Hg, there was no family history of glaucoma, and stereo disc photographs were graded as normal. Visual field screening was normal. Results on ophthalmologic examination were normal, and there was no history of eye injuries, surgery, or ocular disease. Only 28 of the 43 normals took the special letter acuity test, but the age distribution (mean, 57.2 ± 12.6 years) was not statistically different from that of the patients with glaucoma in this sample.

Short-Wavelength Automated Perimetry

For SWAP, we used a modified Humphrey Field Analyzer as described by Johnson et al.[4] An auxiliary background lighting source was installed on either side of the perimeter adjacent to the original light sources. An 80 W Kodak carousel projector bulb (ELS; Eastman Kodak, Rochester, NY) was mounted behind heat-absorbing glass, and a yellow Schott OG530 filter (530 nm cutoff) was used to provide a background luminance of 200 cd/m^2. A size V short-wavelength target was presented by placing an OCLI 500 nm cutoff filter (peak wavelength, 450 nm) (Optical Coating Laboratories, Santa Rosa, CA) in front of the projection arm. Lens density corrections were not performed on the data. Threshold values, but not global indices, were obtained.

High-Pass Resolution Perimetry

For HRP, the Ophthimus Version 1.0 perimeter (High Tech Vision, Malmo, Sweden) was used. Standard printouts providing ring scores for all test locations were generated, with quadrant mean ring scores and global indices. The global indices are similar to those obtained with Humphrey and Octopus perimeters. Global deviation represents a mean deviation of all points compared to age-matched normals. Mean retest change is similar to short-term fluctuation. Adjusted local deviation is a statistical attempt to define the degree of localized change within the field similar to corrected pattern standard deviation. In addition, a calculation of "functional channels" is made. This score attempts to quantify the ganglion cell density by determining receptive field sizes for the individual points based on the minimum angle of resolution of the detected stimulus at that point. The value for each point is summed across the field and expressed as a percentage of the age-corrected average normal sum.[45]

Motion Detection Threshold

This test was a simplified version of that described by Silverman et al.[22] The test uses a field of randomly positioned dots, presented on successive display frames on a computer-controlled display monitor. A proportion of the dots appears in a new set of randomly chosen locations, whereas the remaining dots move coherently to either the left or the right. The test estimates the minimum proportion of coherently moving dots required for the direction of motion to be correctly identified by the patient. Patients viewed the display monitor monocularly, at a distance of 60 cm, with an appropriate refractive correction. The random dots appeared in a square field of 16° × 16°, and each dot consisted of a 2 × 2 block of screen pixels subtending an angle of approximately 4.3 arc min. The dots were white, with the maximum brightness that could be produced by the display (88 cd/m^2), whereas the background was dark (0.1 cd/m^2), providing close to 100% contrast. Frames were presented at a rate of 11.5 Hz, with 100 dots in each frame. The coherently moving dots had a velocity of 6.4°/second (15 pixels per frame). A two-alternative forced choice procedure, in which the observer had to choose either left or right as the direction of motion, was used to estimate thresholds. The direction of motion and the percentage of coherently moving dots was varied randomly from trial to trial. This percentage had one of 11 values (0%, 3%, 7%, 12%, 18%, 26%, 34%, 43%, 53%, 64%, and 72%). Each of these conditions was presented on average 16 times (the exact number varied because of the random choice of stimulus conditions), and the total number of presentations used for each threshold determination was 176. The display time was 1 second, with an infinite response time allowed, but a choice was always required. There was then a delay of 0.75 seconds before the next stimulus presentation.

Threshold was determined by probit analysis of the resultant psychometric function, with the threshold defined as the percentage of coherently moving dots at which responses were estimated to be correct on 83% of presentations. The essential differences from the technique described by Silverman[22] were that in our test, only the central 16° of visual field was included (compared to 60°), a two-directional rather than a four-directional choice was presented, and threshold was defined as 83% correct responses rather than 75%.

Contrast Sensitivity

Contrast sensitivity was recorded for stationary, phase-reversing sine wave gratings, sinusoidally flickered in counterphase at 25 Hz. Patients viewed a Sony Trinitron Multiscan HG monitor (Sony, Tokyo, Japan) monocularly in a dimly lit room at a distance of 1 meter, with appropriate refractive correction. A VSG2 display board (Cambridge Research Systems, Cambridge, UK) controlled by the program Psycho V2.4 (Cambridge Research Systems) was used to generate the gratings and to run the tests. The test area was a circle, 2° in diameter, displayed against a spatially and temporally uniform background with a luminance equal to the mean luminance of the test area (approximately 50 cd/m^2). The method of limits was used to determine threshold contrast at 0 cycles/degree (screen grating with uniform luminance). A black fixation cross, 0.25° wide, was present in the center of the test patch. Patients were instructed to look steadily at the cross and to decrease the contrast of the grating to the point at which it was was no longer visible against the background. This determination was re-

peated four times at each spatial frequency (0, 2, 5, 8, and 10 cycles/degree), and the log of the mean contrast of these settings was then recorded as the threshold for each spatial frequency.

Static, Flickering, and Equiluminant Letter Acuity Tests

These tests (designed by Michael Fendick, PhD) are described in detail in a separate publication.[46] The monitor and test conditions were as for contrast sensitivity above. Contrast thresholds for correct identification of static or flickering letters of white, grey, or blue were measured. The subject's threshold contrast (or threshold modulation depth) was determined for a single 6/60 letter randomly presented in one of five positions: at fixation or at 3° eccentricity along the 0°, 90°, 180°, or 270° visual field meridians. Subjects were instructed always to direct their gaze at a fixation target in the center of the display screen. Stimuli were one of seven Sloan letters (D, E, F, H, N, O, and Z). In the "static" tests, the letter was displayed in negative contrast for 200 msec presentation. For the flickering letter tests, the luminances of the letter and background were counterphase modulated in a square wave pattern at 25 Hz for 200 msec presentation. Other aspects of the testing procedures were identical for flickering and static tests. Contrast thresholds were determined using a modified binary search technique.[47]

Heterochromatic flicker photometry was then used to measure the equiluminant point for a green letter against a white background; after that, the visual acuity for a green letter at the measured equiluminant point was determined (attempting to target the P-cell pathway). Subjects were instructed to observe the fixation target in the center of the display screen while reporting their perception of a peripheral green test spot. The method of limits was used with bracketing to estimate the luminance required to null the subject's percept of flicker and/or to render the green spot minimally visible at each position. Because equiluminant points can differ significantly between persons, as well as between different retinal locations within persons, the subject's equiluminant point at each of the four 3° eccentric stimulus positions was measured. Using these equiluminance values, acuity measurements for equiluminant green letters were obtained at each of the four 3° eccentricities along the 0°, 90°, 180°, and 270° visual field meridians. Critical visual angle for the letters ranged from 2.51 to 50.12 arc min (i.e., −6/15 to −6/300) in 0.1 log unit steps.

For data analysis, the raw contrast thresholds were expressed as the logarithm of threshold contrast, where contrast is defined as $(L_{stimulus} - L_{background})/(L_{stimulus} + L_{background})$, where L is luminance in cd/m^2. For the equiluminant acuity tests, acuity, measured in arc min, was similarly converted by taking the logarithm.

Pattern Electroretinogram Recording

A UTAS-E 2000 system (LKC Technologies, Gaithersburg, MD) was used for PERG and ERG recording. Details of our central PERG recording technique have been reported elsewhere.[37] In brief, two standard 1 cm gold-plated cup electrodes (Grass Instrument, Quincy, MA) were used—one placed on the central forehead (ground) and the other on the ipsilateral temple posterior to the lateral canthus. For ERGs, the reference electrodes were changed to ECG electrodes (Ag/AgCl; Lifetrace, Gananoque, Ontario, Canada). Local anesthesia (proparacaine hydrochloride, 0.5%) and a Carter–Hogg-style gold foil electrode (The Electrode Store, Enumclaw, WA) were used. Electrode resistance was measured with a digital multimeter before insertion and was less than 4 Ω. Each gold foil electrode was used for a maximum of five subjects and then was discarded. We have reported that the gold foil protocol produces reproducible data for both flash ERG[48] and PERG recording.[37]

For PERGs, the subject sat in a chair 80 cm away from the television screen and fixed binocularly on a 6 mm spot at the center of the screen. The subject's distance refraction was worn using perimetric size lenses with appropriate near addition, depending on age (usually 1 to 1.25 D). A white card (1 m × 0.8 m) surrounded the television monitor and was illuminated by an overhead incandescent 60 W spotlight, creating a surround luminance of 20 cd/m^2. The mean luminance of the television screen was 200 cd/m^2. Contrast was maximized (99%). Luminance recordings were performed with a radiometer–photometer (model 550; E. G. & G., Salem, MA). Each PERG from a pattern stimulus was the average of 200 accepted responses, with two sets of 200 then off-line averaged. An example of a PERG trace is shown in Figure 1.

Artifact reject limits were set at 20 μV, and trace sampling time was 150 msec. Bandpasses were set at 1 Hz and 70 Hz. The television monitor was 23.3 cm high × 29.4 cm wide (16.6° × 20.8° at 80 cm viewing distance). The monitor was 60 Hz, pattern reversal was temporally square wave, and reversals were locked to the periods between frames. The check size was 7 mm (30 minutes) and the frequency used was 3.75 reversals per second (1.875 Hz) to record transient PERGs. Amplitudes and peak times were measured relative to baseline and to stimulus onset for the positive wave occurring at approximately 50 msec (P50 or P1) and for the second negative wave occurring at approximately 95 msec (N95 or N2). The "baseline correct" function of the UTAS 2000 software (LKC Technologies) was used only when determining indi-

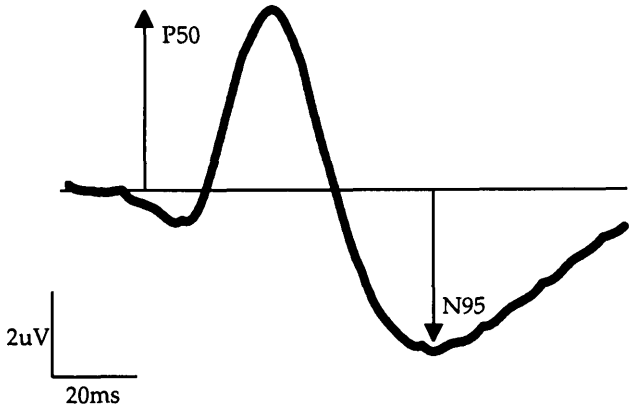

FIGURE 1. Example of transient pattern electroretinogram (PERG) recorded from a normal patient. The P50 and N95 components are demonstrated.

vidual P1 versus N2 values if there was any apparent drift in the baseline. This analysis function uses a least-squares linear regression through the data and adjusts for baseline drift. The baseline correction function was not used for P50 + N95 amplitudes.

Electroretinogram Recording

Flash ERGs were recorded after the PERG, with pupils dilated to a minimum of 8 mm. Conditions were standard[49] except that gold foil electrodes and signal averaging were used. A semiautomated Ganzfeld stimulator provided a strobe flash stimulus of 1.99 cd/m^2 · second. The photopic intensity series was recorded first to ensure fully light-adapted conditions[50] and was followed by 20 minutes of dark adaptation before scotopic responses were recorded. The amplifier bandpass was set between 0.3 to 1500 Hz for ERGs, and the low cut was increased to 75 Hz for recording OPs under photopic and scotopic conditions. Photopic background luminance was 25 cd/m^2; additional nonstandard recordings were taken using a bright background of 155 cd/m^2.

For photopic ERGs, each final trace was derived from the average of 20 ERG waveforms, recorded with a 1-second interstimulus interval. Traces were recorded at 0, 0.2, 0.6, 1.0, and 1.4 log units of attenuation (LU) filtered flash stimulus. Scotopic ERGs were recorded with a 0 LU and 2.4 LU filtered flash stimulus, with traces derived from 10 averaged waveforms of 5-second interstimulus intervals. Each trace was visualized on the screen first and then averaged if acceptable. Manual rejects were used if there was any clear blink contamination not automatically rejected. The a-wave amplitudes were measured relative to baseline, and b-wave amplitudes were determined from a-wave trough to b-wave peak. Latencies for a and b waves, relative to stimulus onset, also were recorded. For OPs under photopic and scotopic conditions, the amplitude sum of the first four positive and the first four negative peaks was calculated.

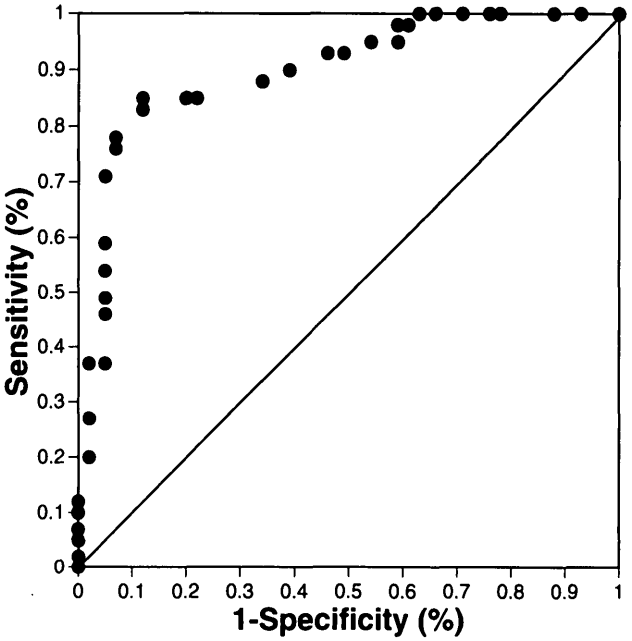

FIGURE 2. Example of receiver operating characteristic curve for a test with a high A_z score (0.898)–pattern electroretinogram N95 amplitude. This provides good separation between normals and patients with glaucoma.

Analysis

Statistics. Receiver operating characteristic analysis[51] was performed on continuous variables derived from each of the tests. The program was written on SPSS (SPSS Inc., Chicago, IL; 1993). We plotted an ROC curve, which graphs sensitivity versus 1 − specificity for each possible cutoff point across the measurement range for each of the variables. Sensitivity refers to the ability of a test to detect glaucoma, whereas specificity confirms test results that correctly find a normal response when glaucoma is not present.

We then calculated the area under the ROC curve (termed A_z) according to the method of Hanley and McNeil.[52] A_z represents the aggregate goodness of the parameter in separating normals from patients with glaucoma. The A_z score is not dependent on the shape of the curve and is, therefore, a better overall indicator than d′ (the distance between the diagonal from 100% sensitivity to 0% specificity, to the interception of the ROC curve). The d′ is more dependent on the ROC curve shape. Figures 2 and 3 show examples of ROC curves for a test with a high A_z score (PERG N95 amplitude) and a low score (photopic OP sum).

Optimal cutoff points associated with the lowest general error rate (GER) were then derived. The GER refers to the percentage of individuals misclassified when a specific cut-off point is used to arbitrate be-

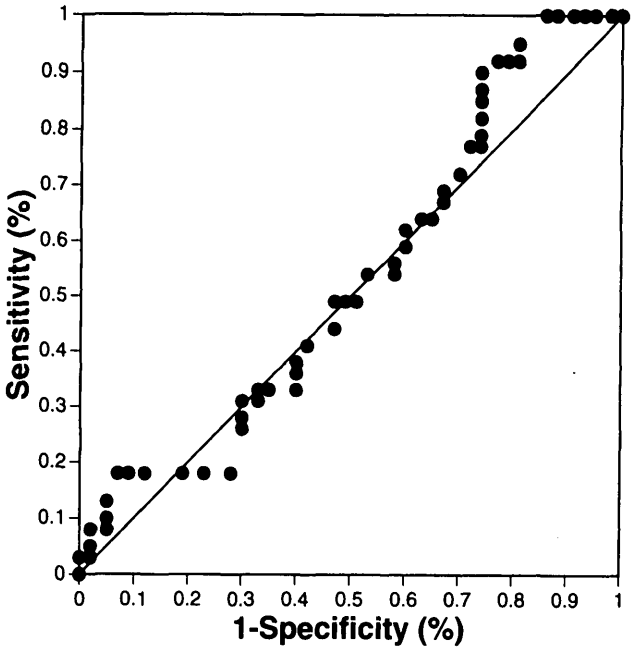

FIGURE 3. Example of receiver operating characteristic curve for a test with a low A_z score (0.522)—photopic oscillatory potential sum. This test provides poor discrimination, little better than chance.

tween normal and abnormal. These cases represent false negatives and false positives.

There were 86 parameters analyzed in the ROC analysis. The parameters chosen were, in most cases, standard variables which we felt were most representative of the information obtained from the tests. For SWAP the foveal threshold, the four primary points (at 9° horizontally and vertically from fixation) and four total quadrant scores were analyzed. For HRP, global indices (including functional channels) and quadrant mean ring scores were examined. The motion detection test provided a single motion detection threshold value. For each of the letter acuity tests, logarithms of contrast thresholds at the fovea and four meridians were available for analysis, while the equiluminant test provided data from the four meridians only. For the PERG, P50 and N95 amplitude and latency and P50 + N95 amplitude were included. Due to the large amount of flash ERG data collected, not all parameters were included. A representative cross-section of the intensity series included values for a and b wave latencies and amplitudes from 0.0 LU bright background photopic ERG, 0.0 LU photopic ERG, a semisaturated 0.6 LU photopic ERG, and scotopic ERGs at 0.0 LU and 2.4 LU attenuation. Photopic 30 Hz flicker amplitude and peak time, and photopic and scotopic OP sums were also included.

RESULTS

The ROC analysis determined the area under the ROC curve (A_z), optimal cut-off point, sensitivity, specificity, and general error rate (GER). Results are presented in Tables 1 and 2. Of all parameters, the pattern ERG performed the best. The amplitude of N95 gave the highest A_z score (0.898) and a low GER of 13.4% (see Fig. 2). This represents a sensitivity of 85.4% and a specificity of 87.8%, so the PERG appears to provide fairly good discrimination between normals and patients with early glaucoma. The amplitude sum P50 + N95 had a lower A_z score of 0.873, GER 20.7%. P50 amplitude and latencies for both components were not good markers. Single psychophysical parameters with high A_z scores and low GER were SWAP superonasal quadrant total (0.833, 23.5%) and HRP superonasal quadrant mean (0.827, 22.5%). Inferonasal quadrant scores for both tests were similar, with GERs approximately 25%. Temporal quadrants for both tests had slightly lower scores. Even the SWAP nasal field primary points had reasonable scores considering that they tested only one point, with the least sensitive the superotemporal primary point (0.683, 34.6%). For the HRP global indices, global deviation and functional channels scored well (GER 23.8% for both), whereas adjusted local deviation did not (GER 40%).

Many of the letter acuity tests had A_z scores > 0.75. Of the 34 different letter tests examined, the flickering letters presented in the superior field (90° position) and the equiluminant letters gave consistently higher A_z scores with better resultant sensitivity and specificity. The best was the equiluminant letter at 90° (0.898, 14.5%).

Motion detection threshold scored poorly; it was little better than chance for identifying the patients with glaucoma. Flicker contrast sensitivity was poor for all six frequencies tested.

None of the flash ERG parameters had A_z scores above 0.7, so their corresponding GERs were high. Bright background photopic recording conditions (155 cd/m^2) did not demonstrate any advantage over normal photopic conditions. Most flash ERG latency and amplitude measures did reflect some changes with glaucoma, but these did not provide good discrimination. Flicker peak time (30 Hz) and amplitude scored poorly, and oscillatory potentials were disappointing under both photopic (Fig. 3) and scotopic conditions.

The six patients with glaucoma in whom the Humphrey field did not show a confirmed defect that met the criterion for a scotoma are of special interest. They had a MD on their most recent Humphrey field ranging from +1.78 dB to −0.66 dB. Test results examined in these six patients showed that when the ROC cutoff points were applied to each patient, abnormalities were seen on many of the tests. For the PERG, all six had a reduced N95, and 4 of 6 had a reduced P50 + N95. All had abnormal SWAP superonasal quadrant scores, and 4 of 6 had at least one other abnormal

TABLE 1. Receiver Operating Characteristics Analysis Summary for Psychophysical Tests

Test Parameter	*A_z Score*	*Cut-off*	*Sensitivity (%)*	*Specificity (%)*	*General Error Rate (%)*
SWAP					
Foveal threshold	0.695	24 dB	42.9	89.7	34.6
Quadrant totals					
Superonasal	0.833	391 dB	100.0	51.3	23.5*
Superotemporal	0.761	397 dB	42.9	89.7	34.6
Inferonasal	0.799	380 dB	73.8	74.4	25.9
Inferotemporal	0.721	417 dB	85.7	48.7	32.1
Primary points					
Superonasal	0.746	21 dB	64.3	74.4	30.9
Superotemporal	0.683	17 dB	45.2	87.2	34.6
Inferonasal	0.755	23 dB	71.4	74.4	27.2
Inferotemporal	0.695	26 dB	83.3	46.2	34.6
HRP					
Global deviation	0.809	−0.15 dB	85.4	66.7	23.8*
Adjusted local deviation	0.601	0.52	48.8	71.8	40.0
Functional channels	0.831	81%	82.9	69.2	23.8*
Quadrant means					
Superonasal	0.827	3.7	87.8	66.7	22.5*
Superotemporal	0.782	4.0	80.5	66.7	26.3
Inferonasal	0.815	4.7	70.7	79.5	25.0*
Inferotemporal	0.748	3.6	87.8	53.8	28.8
Motion detection threshold	0.556	23%	41.9	79.5	40.0
Flicker contrast sensitivity					
0 cyc/deg	0.606	0.61	38.1	84.6	39.5
2 cyc/deg	0.600	0.45	28.6	94.9	39.5
3 cyc/deg	0.574	0.45	30.2	94.9	39.0
5 cyc/deg	0.559	0.32	22.3	92.3	43.9
8 cyc/deg	0.559	0.35	51.2	64.1	42.7
10 cyc/deg	0.564	0.35	53.5	59.0	43.9
Letter acuity tests					
White static, fovea	0.664	−1.50	58.5	64.3	39.1
0°	0.626	−1.50	87.8	28.6	36.2
90°	0.779	−1.11	73.2	75.0	26.1
180°	0.616	−1.50	87.8	32.1	34.8
270°	0.658	−1.33	65.9	57.1	37.7
White flicker, fovea	0.745	−1.03	75.6	71.4	26.1
0°	0.721	−1.11	92.7	39.3	29.0
90°	0.823	−0.70	80.5	78.6	20.3*
180°	0.727	−1.03	90.2	39.3	30.4
270°	0.810	−0.90	92.7	53.6	23.2*
Blue static, fovea	0.630	−1.36	100.0	14.3	34.8
0°	0.651	−1.06	58.5	71.4	36.2
90°	0.723	−0.88	63.4	75.0	31.9
180°	0.670	−1.18	92.7	32.1	31.9
270°	0.679	−1.18	92.7	25.0	34.8
Blue flicker, fovea	0.731	−0.22	70.7	71.4	29.0
0°	0.823	−0.35	97.6	64.3	15.9*
90°	0.814	−0.30	95.1	53.6	21.7*
180°	0.786	−0.37	87.8	60.7	23.2*
270°	0.749	−0.29	80.5	67.9	24.6*
Grey static, fovea	0.567	−1.12	39.0	75.0	46.4
0°	0.613	−1.12	53.7	64.3	42.0
90°	0.709	−0.95	61.0	75.0	33.0
180°	0.659	−1.12	68.3	67.9	31.9
270°	0.614	−1.12	65.9	50.0	40.6
Grey flicker, fovea	0.716	−0.82	95.1	25.0	33.3
0°	0.708	−0.82	100.0	17.9	33.3
90°	0.858	−0.23	75.6	82.1	21.7*
180°	0.735	−0.59	90.2	46.4	27.5
270°	0.774	−0.53	87.8	53.6	26.1
Equiluminant letter tests					
Letter size 0°	0.745	10.0	92.7	46.4	26.1
Letter size 90°	0.898	12.59	100.0	64.3	14.5*
Letter size 180°	0.747	10.0	90.2	35.7	31.9
Letter size 270°	0.824	12.59	87.8	64.3	21.7*

The A_z score represents the area under the receiver operating characteristics curve in which an A_z of 0.5 represents chance discrimination between normal subjects and patients with glaucoma, whereas an A_z of 1.0 represents perfect discrimination. Sensitivity, specificity, and general error rate (GER; percent misclassified) are given for cut-offs in the measurement scale yielding minimum GER.
* Parameters with GER ≤25%, implying better discrimination.
SWAP = short-wavelength automated perimetry; HRP = high-pass resolution perimetry.

TABLE 2. Receiver Operating Characteristics Analysis Summary for Electrophysiology Tests

Test Type	*A_z Score*	*Cut-off*	*Sensitivity (%)*	*Specificity (%)*	*General Error Rate (%)*
Pattern ERG					
P50 amplitude	0.709	3 μV	58.5	73.2	34.1
P50 latency	0.547	47 ms	19.5	92.7	43.9
N95 amplitude	0.898	−2.3 μV	85.4	87.8	13.4*
N95 latency	0.699	93.6 ms	70.7	70.7	29.3
P50 + N95	0.873	5.1 μV	73.2	85.4	20.7*
Photopic ERG					
0.0 LU					
a wave amplitude	0.624	−46.0 μV	59.0	62.8	39.0
a wave latency	0.605	14.0 ms	84.6	44.2	36.6
b wave amplitude	0.586	182 μV	79.5	46.5	37.8
b wave latency	0.612	30.5 ms	61.5	60.5	39.0
0.6 LU					
a wave amplitude	0.700	−26 μV	76.9	60.5	31.7
a wave latency	0.610	16.8 ms	43.6	79.1	37.8
b wave amplitude	0.575	69 μV	48.7	67.4	41.5
b wave latency	0.613	30.6 ms	35.9	83.7	39.0
0.0 LU (bright background)					
a wave amplitude	0.646	−24.0 μV	67.5	62.8	34.9
a wave latency	0.568	14.8 ms	45.0	69.8	42.2
b wave amplitude	0.595	122.0 μV	85.0	37.2	39.8
b wave latency	0.649	27.5 ms	32.5	88.4	38.6
30 Hz flicker					
Amplitude	0.651	127 μV	79.5	53.5	34.1
Peak time	0.540	29.5 ms	51.3	60.5	43.9
Photopic OPs sum					
Normal	0.522	80 μV	17.9	93.0	42.7
Bright background	0.555	62 μV	25.0	90.7	41.0
Scotopic ERG					
0.0 LU					
a wave amplitude	0.659	−208 μV	51.4	77.5	34.7
a wave latency	0.597	17.2 ms	40.0	87.5	34.7
b wave amplitude	0.616	392 μV	57.1	67.5	37.3
b wave latency	0.678	51.4 ms	48.6	82.5	33.3
2.4 LU					
b wave amplitude	0.629	210 μV	60.0	67.5	36.0
b wave latency	0.677	51.4	48.6	82.5	33.3
Scotopic OPs sum	0.621	180 μV	57.1	67.5	37.3

ERG = electroretinogram; OPs = oscillatory potentials.

quadrant and a reduced foveal threshold. For HRP, 4 of 6 had increased global deviation, and 4 of 6 had reduced functional channels; all patients had at least one abnormal global index. High-pass resolution perimetry mean quadrant ring scores were reduced in 5 of 6 patients in at least two quadrants, and the remaining patient was still above the cutoff in all four quadrants. Five of six patients had more than 10 abnormal values for static, flickering, and equiluminant letter acuity tests. Only 2 of 6 had abnormal motion detection, and only 3 of 6 had abnormal flicker contrast sensitivity results (in each case, 8 cpd and 10 cpd). Most ERG values were normal.

DISCUSSION

The purpose of this study was to examine how a large variety of psychophysical and electrophysiological tests related to glaucomatous damage. The battery of tests was performed on each person and was collected in only two test sessions in close time sequence. This study examined how the tests performed in separating diseased eyes from healthy eyes. Data analysis confirmed that most of the parameters reflected glaucomatous damage to a varying degree, but no single parameter from the psychophysical tests could identify all patients with early glaucoma and still maintain good specificity. What remains to be determined is whether a combination of parameters within a test type—or a combination of tests that use different visual functions—would be useful in detecting early glaucoma or patients at risk for progression to definitive glaucoma. Multiple factor analysis with long-term follow up must be performed to address this possibility.

Many of the newer tests attempted to target the M-cell pathway, but no clear differences were identi-

fied in the performance of these tests over those predominantly targeting the P-cell pathway. We acknowledge that the test conditions used for the flicker contrast sensitivity, motion detection, and letter acuity were not the optimum conditions for separating disease from normal and that the designs of all the tests may not be specific enough to isolate overlapping visual functions.

The performance of SWAP in this study confirms previous reports that it is able to detect early field loss. The fact that quadrant totals or primary points alone, which represent limited samples, achieved sensitivities and specificities in the mid-70% range in the ROC analysis is a good indication that SWAP thresholds are elevated in early glaucoma. It must be emphasized that in addition to the bias induced by having used Humphrey perimetry as a diagnostic criterion, our ROC analysis was limited to continuous variables only (i.e., threshold scores). Direct comparison with Humphrey perimetry based on scotoma criteria was not appropriate in this study, in addition to the bias induced by having used Humphrey perimetry as a diagnostic criterion. However, on standard perimetry, we did observe several patients with early but certain defects who were not identified clearly when the SWAP fields were assessed for scotomas, and a recent report by Flanagan et al[53] had a similar finding.

We deliberately chose not to correct the SWAP thresholds for lens density because current techniques are cumbersome for routine use. In the new Humphrey perimeter, lens density correction is not applied, and Sample[54] found no advantage in correcting for lenticular absorption if appropriate analysis is performed. In this study, we included only patients with good visual acuity because this helped to limit the influence of lens changes. The sensitivity of SWAP could have been improved by a lens density correction, and it could have been improved significantly by a detailed, point-by-point analysis using a larger data base of normals.

High-pass resolution perimetry sensitivities were promising considering that only the global indices and quadrant mean ring scores were examined. In a recent article, we showed that the detection of scotomas by HRP was enhanced by the use of a probability plot,[55] and the Ophthimus version 3.0 software does include a similarly derived plot in its analysis. Therefore, HRP may approach the sensitivity of static threshold perimetry, and its advantages are speed and a high level of patient acceptance.

Results of the motion coherence test and the flicker contrast sensitivity test were disappointing and showed poor sensitivity. We do not recommended using these tests in the form used in this study. Trick recently reported that motion deficits of patients with glaucoma are found most frequently in the central 12°,[56] so the small central field test we used should have been adequate. However, our stimulus parameters differed and may not have been appropriate to detect subtle deficits reliably.

Most of the letter acuity tests showed reductions in patients with glaucoma and achieved reasonable sensitivities. The test design could be improved if test locations were placed away from the horizontal meridian. The letter acuity tests originally were designed to attempt to target M-cell and P-cell pathways separately. Our results were not consistent with a predominant M-cell loss, which has been suggested to occur in early glaucoma.[57,58] The equiluminant letter acuity test showed similar changes to the flickering letter tests. Johnson[59] has proposed the "reduced redundancy" theory to state that selective psychophysical tests may not simply confirm selective losses of one pathway; rather, selecting one system results in less overlap between cell types and their receptive fields, and the ability to detect a functional deficit is enhanced. In addition, one of the criteria for diagnosing patients with glaucoma was abnormal Humphrey visual field results. Hence, our study had a recruitment bias toward patients with established scotomas rather than with early generalized loss, and this may have influenced the findings.

The transient PERG, in particular N95 amplitude, provided good discrimination. This is encouraging because the PERG is an objective test. In this study, we only included a limited sample of two sets of 200 transient reversals at one check size. Steady state recordings with a fast Fourier transformation may have performed even better because of lower variability and superior signal-to-noise ratio.[60] We have shown[37] that PERG amplitudes correlate with visual field indices, and the results here support changes in the PERG in early glaucoma. Abnormal amplitudes were identified at least as frequently as psychophysical test anomalies. If technical problems such as intertest variability[61,62] can be reduced further and if better standardization of PERG recording techniques between centers is established, the use of pattern ERGs in clinical practice may increase. An objective test has significant advantages.

The finding of many patients with early glaucoma and mild reductions and delays in flash ERG parameters is consistent with some previous reports.[35,40,41] These changes support the idea that even in early glaucoma, there can be some outer retinal dysfunction. The changes are not universal, however, and are too small and variable to be clinically useful markers. A recent report concerning experimental glaucoma did not show any changes in the scotopic ERG and OPs except at low thresholds.[63]

One problem with the application of ROC analysis to the data from this study is that psychophysical and

electrophysiological functions decline with age. To minimize this effect, our patient groups were of similar ages. However, the selection of cutoff points will limit the chances for detecting younger patients with glaucoma who start with higher values, and elderly normals will be closer to the cutoff level. Ideally, each parameter could be age adjusted first to increase accuracy; with a larger number of patients, cutoffs could be determined for each decade.

It is possible that data parameters other than those used in the analysis may provide better discrimination. For example, in the perimetric tests, alternative threshold–ring scores or clusters of threshold scores may be more meaningful clinically than the primary points or quadrant data alone. For the ERGs, however, there did not appear to be any difference between the many test conditions covered when these were analyzed individually. For the OPs, a subsequent analysis of individual wavelet amplitudes and peak times showed no significant differences between the two groups.

In the six patients with glaucoma in whom Humphrey field test results failed to show a defect as defined by us, abnormalities were found with many of the tests using the ROC cutoff values. This may imply that some of the psychophysical functions detect abnormalities before white-on-white perimetry becomes abnormal, but this would have to be verified prospectively. These tests then might be a useful addition to standard perimetry in the assessment of suspects. We have tested an additional 90 suspects with the full protocol described above and plan to follow them over time to determine the predictive value of the individual tests.

A major problem with most of the psychophysical tests is the lower specificity and the high false-positive rate, particularly when the test is first performed; this would have to be improved to make the tests clinically useful. None of our subjects had been subjected to a learning test session, although all had perimetric experience with the Humphrey field test and were given introductory demonstrations for the newer tests.

In conclusion, we found that other psychophysical tests could identify most, but not all, patients with early glaucoma—most of whom had a mildly abnormal Humphrey visual field. All these tests reflected glaucomatous damage to varying extents. Tests designed to identify predominantly magnocellular or parvocellular losses performed equally in this study. The pattern ERG performed very well, whereas the motion detection test was a poor discriminator. SWAP and HRP were fair considering the limited data used in the ROC analysis. It remains to be seen whether a combination of conventional white-on-white perimetry with one or more of these test techniques would enhance early diagnosis of glaucoma.

Key Words

glaucoma, magnocellular pathway, pattern electroretinogram, perimetry, psychophysical testing

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