The S-Cone PhNR and Pattern ERG in Primary Open Angle Glaucoma

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Purpose. To compare the sensitivity of the photopic negative response (PhNR) from the shortwave (S)-sensitive and the long (L)- and medium (M)-wave–sensitive cone electroretinograms (ERGs), with the pattern electroretinogram (PERG) in the early stages of primary open-angle glaucoma (POAG).

Methods. Eighteen patients under treatment for diagnosed POAG and 19 normal control subjects were investigated. S-cone ERGs were elicited using adaptation to 650-nm light to suppress L-cone activity, and substitution between 450 nm and 535 nm to silence M-cone response at luminances higher than rod saturation. PhNRs from the L&M-cone pathways were elicited by a 200-msec pulse of red light (650 nm) on a continuous blue (450 nm) background. PERGs were recorded in accordance with the International Society for Clinical Electrophysiology of Vision (ISCEV) standard.

Results. Each method showed a statistically significant difference in the two groups. The S-cone PhNR was the most sensitive test and provided the most statistically significant results, with the largest area enclosed by the receiver operating characteristic (ROC) curve.

Conclusions. The findings indicate that all three types of ERG may be useful in glaucoma investigation. The L- and M-cone PhNRs may have a role in monitoring established glaucoma. The previously reported high sensitivity of the PERG was confirmed. Extensive diffuse damage to S-cone bipolar and bistratified ganglion cells appears to occur at a very early stage in POAG, owing to a pressure-related mechanism, and the S-cone PhNR was the most sensitive test. It may in future have an important role in diagnosis and monitoring of early glaucoma. Further investigation of this possibility is recommended. (*Invest Ophthalmol Vis Sci.* 2001;42:1266–1272)

Electroretinography (ERG), has received little attention in literature on the changing definition of glaucoma.[1] However, the pattern ERG (PERG) is a sensitive indicator of glaucomatous damage.[2–4] Indeed, it might be argued from results in some studies that the PERG is the most sensitive of all tests.[3,4] Whereas the PERG reflects diffuse central damage,[5] the multifocal ERG has been developed as an objective correlate of perimetry.[6] By contrast, the a- and b-waves of the conventional ganzfeld ERG have been reported to be relatively insensitive in early primary open-angle glaucoma (POAG),[4,7] but recent developments prompted us to initiate a comparison of ganzfeld ERGs obtained by newer techniques. In particular, as a result of innovative studies in experimental glaucoma,[8] attention has been directed to the photopic negative response (PhNR).[8] This negative (N) wave (N100) may be compared with the N95 of the PERG, which has been considered to be associated with ganglion cell[9] or optic nerve[10] function.

Several types of negative ERG waves, of proximal origin, including those just described may be affected in glaucoma,[3,4,8,11,12] but the recently described PhNR, the negative wave after the b-wave in response to a red flash on a blue background is of particular interest. It is presumed to relate only to the long (L)- and medium (M)-wave–sensitive cone pathways. Viswanathan et al.[8] showed from extensive studies on primates that this potential is reduced in the early stages of experimental glaucoma. It is also reduced pharmacologically by tetrodotoxin (TTX), indicating that it relates to activity in the proximal layers of the retina. It has been hypothesized[8] that the PhNR may originate from spiking activity in amacrine and ganglion cells and their axons, with some possible involvement of glial cells of the retina to explain its extended time course. The PhNR signal may be acquired quickly, even in the absence of clear media. A recent study reported this test to be potentially useful in glaucoma and ocular hypertension assessment, although less sensitive than the PERG.[13]

The blue-sensitive mechanism is frequently impaired in the early stages of POAG[14,15] and is investigated clinically by short-wavelength automated perimetry (SWAP).[16–18] However, SWAP may be subject to variability due to the subjective nature of the task and to intraocular scattered light.[17,18] An electrophysiological approach, which avoided the problems inherent in psychophysical testing and was less affected by light scatter, might therefore provide an attractive technique. Glaucomatous damage has been considered to be confined to ganglion cells,[19] and, therefore, until the recent discovery of the proximal component in the ganzfeld ERG,[8] it seemed unlikely that the shortwave-sensitive (S) cone ERG would be a good method of investigation for POAG. For this reason attention was focused on the visual evoked cortical response to a blue grating on a yellow background, which would primarily depend on ganglion cell function and this was found to be affected in glaucoma.[20] However, given the possibility that we could now record an S-cone PhNR, this appeared an interesting proposition for several additional reasons.

It had been a longstanding puzzle as to whether the damage to the blue color mechanism is truly selective damage, or whether it appears so because of a phenomenon of sampling in a system of sparsely distributed detectors.[21] Tests involving small perimetric stimuli or gratings may not provide convincing evidence of selective damage, and evidence that the loss is nonselective continues to accumulate.[22] By comparing the PhNR, elicited from S-cone and L- and M-cone (L&M-cone) pathways, this question might be resolved.[23]

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The site of functional damage to the S-cone pathway has not yet been clearly established in glaucoma, and, again, the ERG can help to elucidate this.[23] The pathway primarily involves the S cones,[24] S-cone bipolar cells, and the bistratified midget ganglion cells.[25] In the L&M-cone systems, damage is expected to occur at the ganglion cell and nerve fiber level, producing the classic forms of localized defect,[26] although diffuse damage can occur.[26,27] However, in the S-cone pathway, it is conceivable that the damage may be distributed differently.

S cones differ from L and M cones in many respects. They have more permeable membranes,[24] higher metabolic requirements, and are therefore more vulnerable to damage and more sensitive to hypoxia and ischemia.[15,28] This may relate to the classic rule of Kollner,[29] which asserts that acquired defects in the blue-sensitive mechanism relate to malfunction in the distal, rather than the proximal, layers of the retina.

The frequent finding of tritanopic defects in central vision in glaucoma[14,15] is consistent with the idea that there is diffuse damage to the S-cone system in addition to arcuate scotomata that relate to axonal damage. In the L- and M-cone systems, it is also now accepted that diffuse damage is more common[27] than was formerly supposed.[26,30] Quantitative models of ganglion cell receptive field density[31,32] show that the ganglion cells in the areas sampled by the criteria for detection of early POAG[4] could only account for a small proportion of the total amount of neural damage in early glaucoma.[33] Furthermore, the high sensitivity of the PERG,[3,4] which is derived predominantly from central fields where there are few scotomata in POAG, demonstrates the virtually universal presence of central diffuse damage.[5]

If significant diffuse damage occurs in the S-cone system, a coinciding, early, localized defect in the proximal layers would result in a combined loss of sensitivity. This would therefore be the defect most easily detected by SWAP, accounting for reports that the first sign of S-cone dysfunction is a localized scotoma[34] and thus perhaps misleadingly relating S-cone pathway dysfunction purely to ganglion cells and their axons. Diffuse damage in the distal and intermediate layers would be more easily detected by ERG. The a- and b-waves of the conventional photopic ERG are believed to arise predominantly from activity in the receptors[35,36] and bipolar cells,[36] and from the foregoing discussion, it may be seen that it is also possible to monitor activity in the proximal layers by the PhNR. The a-, b-, and PhNR waves of the ERG may therefore primarily reflect activity in the three successive neurons in the direct retinal pathway. Contributions from other neurons may occur to disrupt this simple relationship,[7,36] but their influence is minimized at photopic luminances with temporally extended stimuli,[36] particularly in the case of the S-cone ERG, where there is less evidence of amacrine and hyperpolarizing bipolar activity.

Although S-cones comprise less than 0.5% of the receptors in the retina, several methods of exciting them selectively and obtaining satisfactory ERGs have been described.[37–41] The S-cone ERG has a small negative a-wave and a prominent positive b-wave, followed by a negative-going deflection, which, if recorded at low stimulus frequencies (<2 Hz), may extend to a trough of negative polarity, the S-cone PhNR. It is logical to suppose that the waves of the S-cone ERG have corresponding neural origins to those of the L&M-cone ERG. In theory therefore, the S-cone PhNR should have proximal origins similar to those of its L&M-cone counterpart.[8] Given these theoretical considerations we decided to conduct a pilot study on the S-cone and L&M-cone ERGs and the PERG in glaucoma to assess their relative suitability for extended, long-term studies.

Materials and Methods

Eighteen patients with POAG comprised the POAG group (mean age, 65.27 years) and were compared with a group of 19 control subjects (mean age, 60.31 years). Patients and control subjects had clear media and acuity of 20/30 or better in the eye investigated. They were assessed on the 24-2 Swedish interactive threshold algorithm (SITA) standard program on the Humphrey perimeter (Humphrey Instruments, Dublin, CA). The POAG group all had mild to moderate field defects and a history of raised intraocular pressure (IOP) but were currently under treatment. IOPs were measured at the time of testing by an ocular blood flow meter (OBF Laboratories, Malmesbury, UK). The IOPs in the POAG and control groups were not grossly dissimilar, owing to the effect of treatment. The sample construction is further summarized by statistics of age, IOP, and visual field global indices in Table 1. Patients and control subjects participated with informed consent. The project followed the tenets of the Helsinki Declaration and had prior approval of the Bro Taf Ethical Reviews Committee.

PERGs and ERGs were recorded in accordance with appropriate International Society for Clinical Electrophysiology of Vision (ISCEV) standard procedures[42,43] for one eye only, with contralateral corneal reference (CCR) on the unstimulated eye.[44] An averaging system (Medelec Sapphire IV; Oxford Instruments, Eynsham, UK) was used to acquire and process the signals with a filter band-pass of 3 to 50 Hz. Recording began with the PERG[42] with natural pupils. DTL nylon fiber corneal electrodes[45] were placed in the lower fornix of both eyes, in addition to a midfrontal 9-mm silver earth electrode. The subject, wearing an appropriately adjusted refractive correction, viewed a video-generated checkerboard pattern at a distance of 80 cm. The angular subtense of the screen was 16° × 24° with a 19-minute check, reversing four times per second at a mean luminance of 105 candelas (cd)/m^2 and a 95% contrast. A series of 250 responses were averaged.

For ganzfeld ERGs,[43] the subject's pupil was then dilated using 1% tropicamide, and a miniature ganzfeld LED stimulator (CH Electronics, Bromley, UK) was used to obtain the remaining ERGs. To record the L&M-cone ERG, including the PhNR, a stimulus protocol based on the method of Viswanathan et al.[8] was used. The response to a 200-msec red (650 nm) pulse at 2500 trolands (td) was recorded at 1.8 Hz, on a continuous blue (450 nm) background at 92.5 td. After 1 minute of preadaptation to the blue light, an average of 200 responses was recorded.

To obtain the most analytical results, we required prolonged stimulation showing separate ON and OFF potentials. Using the simple background-adaptation method, we found that OFF potentials were often present, indicating a contribution from L&M-cone pathways. The S-cone ERG was therefore recorded using a technique of silent substitution in addition to background adaptation,[23] based on that used in two previous studies,[38,40] but with a longer wavelength background (650 nm) to provide a more selective suppression of the L-cone response at 5400 td. Alternating blue (450 nm) 1200 td and green (535 nm) light of variable luminance superimposed on the red background was first viewed at 33 Hz to achieve a photometric balance by adjusting the green. At this frequency, rods and S-cones do not contribute

Table 1. Details of Sample Construction

	POAG	Control	*P*
Age (y)	65.27 ± 1.57	60.31 ± 2.8	0.137
IOP (mmHg)	14.63 ± 0.83	14.91 ± 0.68	0.80
Visual field MD	−3.22 ± 0.99	1.26 ± 0.16	0.0001
Visual field PSD	4.76 ± 0.79	1.61 ± 0.09	0.0001

Data are expressed as means ± SE. MD and PSD are visual field indices (Humphrey 24-2 SITA Standard Test; Humphrey Instruments, Dublin, CA).

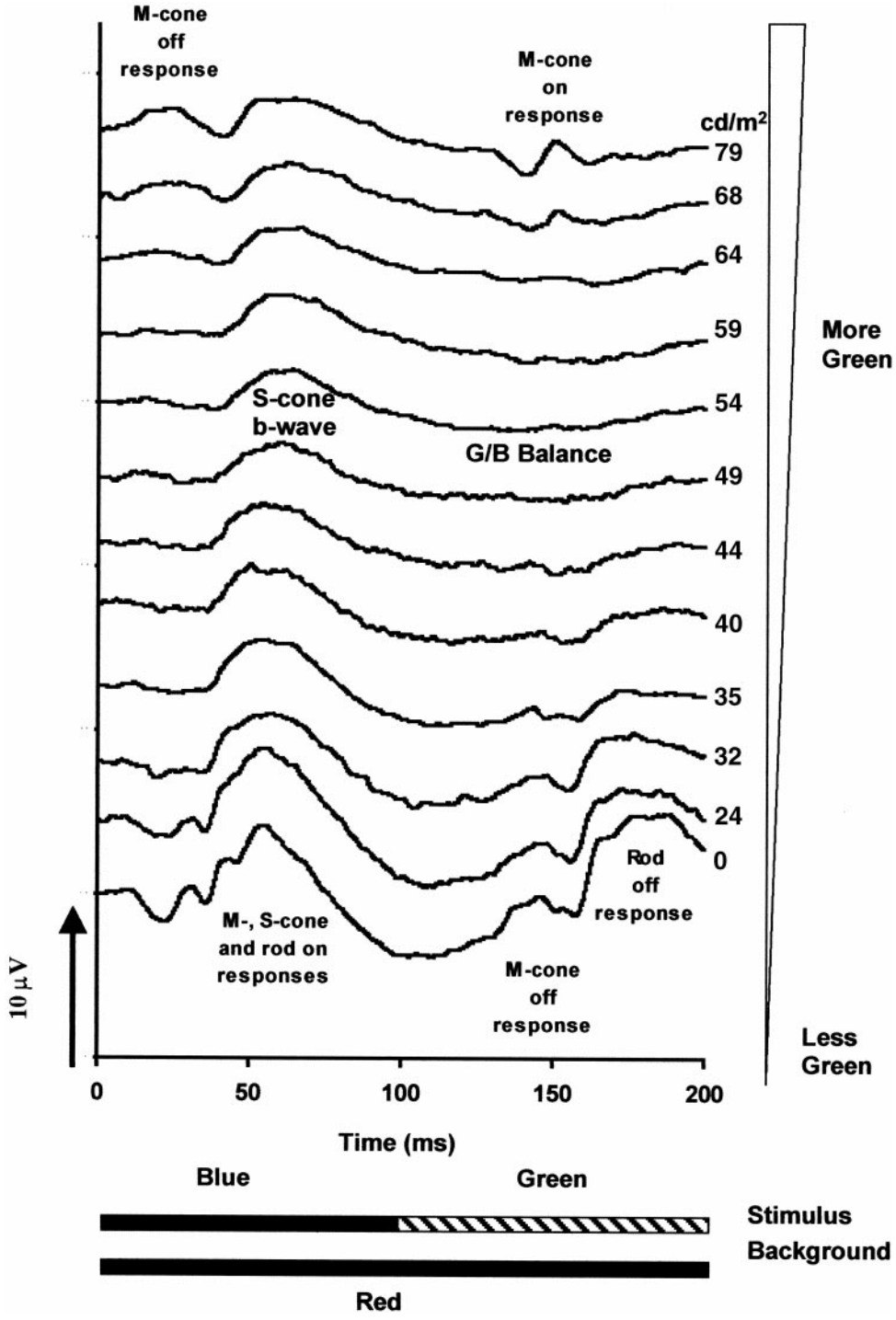

FIGURE 1. The green–blue photometric balance for M cones was determined psychophysically at 33 Hz on a red-adapting field and used at a lower frequency to obtain the S-cone ERG. Because there was no S-cone OFF response, the absence of any response after the blue–green transition indicates that there was no contamination from L- or M-cones. The purity of the S-cone signal was demonstrated by changing the green intensity away from the point of balance. A small increase in green produced M-cone ON responses at the offset of blue. A reduction in green produced M-cone OFF responses at the offset of blue, and further reduction in green reduced the intensity below the rod-saturation level, resulting in rod intrusion. Green-stimulus luminances measured by photometer (model LS110; Minolta, Osaka, Japan).

significantly to the sensation, and the balance is presumed to be correct for the M-cones. The balance point was extremely precise but varied slightly among individuals. When the frequency of this balanced stimulus was reduced, the M-cone output remained silenced, but the S-cones responded vigorously, so that the S-cone ERG could be recorded. The rod response was saturated at the intensities used (>2000 scotopic td,[38,46]), leaving an isolated S-cone ERG that had no OFF response.

The data for each test were analyzed, and the statistical significance of the data was calculated using the *t*-test or Mann–Whitney test, as appropriate. Receiver operating characteristic (ROC) analysis was performed by computer on each electrophysiological test (SPSS software; Chicago, IL) to determine the area under the ROC curve.

RESULTS

Using the described technique, a well-formed S-cone ERG was obtained at frequencies of 4 Hz or less. The absence of any response after the blue–green transition indicates that there was no contamination from L- or M-cones. The purity of the S-cone signal obtained by this method could be demonstrated by changing the green intensity away from the point of balance (Fig. 1). A small increase in green produced M-cone ON responses at the offset of blue. A reduction in green produced M-cone OFF responses at the offset of blue, and a further reduction in green reduced the intensity below the rod saturation level, resulting in rod intrusion. To obtain a large-ampli-

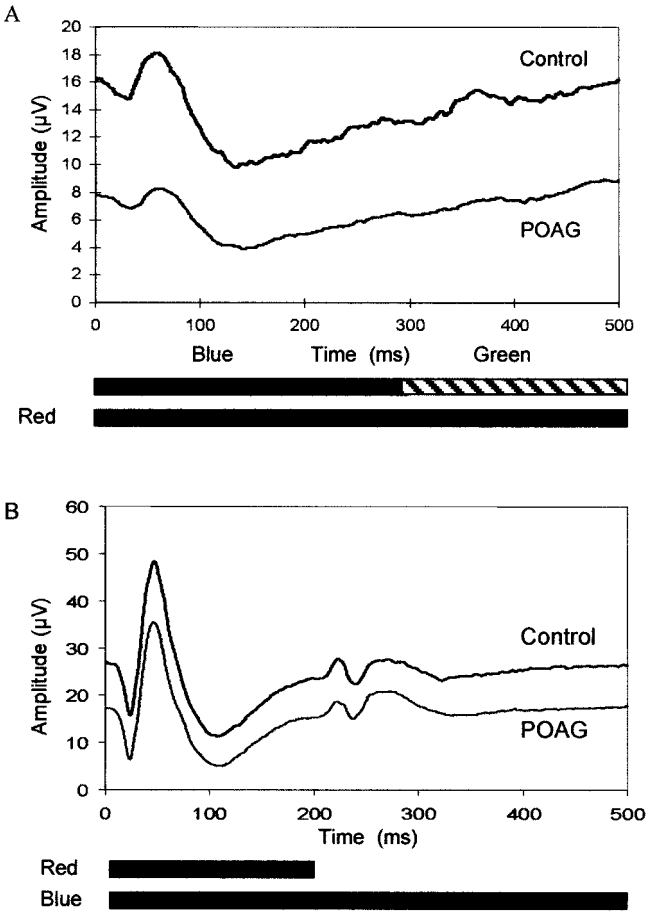

FIGURE 2. (**A**) Group average S-cone ERG at 1.67 Hz for normal control subjects and glaucoma (POAG) groups. (**B**) Group average L&M-cone ERG for normal control subjects and glaucoma (POAG) groups. The highly significant attenuation of the S-cone PhNR compared with the L&M-cone value in POAG, indicates the increased vulnerability of the S-cone system.

tude late negative response (S-cone PhNR) the frequency was reduced to 1.67 Hz.

The group-averaged ERG signals elicited by the three stimulation techniques each had a characteristic waveform in which the small initial negative wave was followed by a major positive-going potential and a larger negative-going potential. (Figs. 2, 3). The a-wave amplitude was measured from the baseline, and the leading edge of the b-wave and PhNR were measured peak to peak. As in previous studies,[2] the latencies were less significantly affected in the POAG group than were the potential amplitudes. Therefore, only amplitude data are presented in the present analysis. The data for each electrophysiological measure, using the three criteria, are shown in Table 2. All three methods produced statistically significant results. The most significant difference between the POAG and the control subjects was achieved with the S-cone PhNR. (P = 0.0001). Similarly, the ROC analysis provided the most favorable ROC area score (0.86) with a sensitivity of 89%, specificity of 74%, and general error rate of 19%, for a cutoff criterion of 5.38 mV. The S-cone PhNR therefore had the best performance, closely followed by the PERG (positive P50–N95). The PhNR (L&M-cone) scored less effectively but still provided a significant indication of diffuse neural damage (Table 2). The only significant correlations of electrophysiologic and perimetric data were between the P50–N95 and the pattern standard deviation (PSD; Spearman's rho, −0.512, P = 0.32), and the S-cone PhNR and mean deviation (MD; Spearman's rho, −0.679, P = 0.002). These two forms of ERG were poorly correlated with each other and may be regarded as relatively independent criteria (Fig. 4).

DISCUSSION

The most intriguing and significant finding in our studies was the performance of the S-cone PhNR compared with the PERG in POAG. The S-cone PhNR is also expected to be less dependent on refractive correction, media transparency, and age of subject. It requires a dilated pupil, although this is a prerequisite for other procedures in glaucoma assessment, and the test would therefore not greatly extend the examination time. Furthermore, the ROC data for this test are probably a conservative indication of its capability, because the samples were in an earlier stage of POAG than in comparable studies (see global indices in Table 1) and did not include cases of POAG with purely diffuse field loss.[4] The attenuation of the S-cone PhNR was consistent with the idea that there is significant damage to bistratified midget ganglion cells. The possibility of involvement of amacrine cells in the generation of the S-cone PhNR cannot be completely excluded.

However, the S-cone ERG, unlike its L&M-cone counterpart, has little or no oscillatory potential, and the opponent receptive fields are coextensive with less lateral inhibition. The low sensitivity of oscillatory potentials in glaucoma generally,[4] compared with our findings in the S-cone ERG, also seems to militate against this possibility. Viswanathan et al.[8] also hypothesized that the sensitivity of the PhNR (L&M-cone) in the early stages of experimental glaucoma could be due to changes in glial cells that precede ganglion cell loss. However, the glial cells are not expected to relate to only one type of ganglion cell, so the different sensitivities of the S-cone PhNR and the L&M-cone PhNR again strengthens the case for the signal arising predominantly from the bistratified midget ganglion cells.

The statistical significance (P = 0.001) and ROC area score of 0.79 for the S-cone b-wave indicates that there is substantial damage to the S-cone bipolar cells in POAG. The major damage in both intermediate and proximal layers must be extensive diffuse damage, to significantly affect ganzfeld ERGs. It is highly improbable that damage to the bipolar cells could be due to trans-synaptic retrograde degeneration, because the S-cone b-wave amplitude was more attenuated than the S-cone PhNR, and histologic studies on focal lesions show damage confined to ganglion cells.[19] The inner nuclear and ganglion cell layers are supplied by the retinal circulation, which, although autoregulated, is evidently affected by the IOP.

It has been suggested that diffuse damage generally[47] and specific dysfunction of the blue color vision[48] may be related

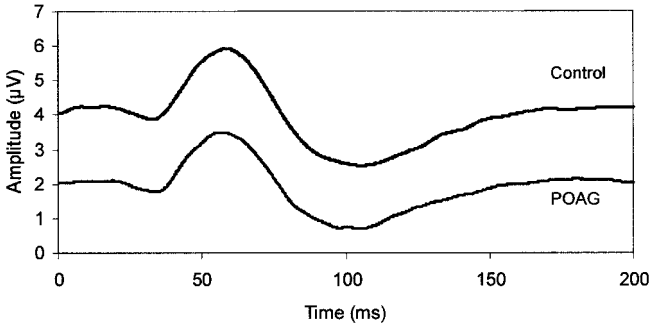

FIGURE 3. Group average PERGs for normal control and glaucoma (POAG) groups.

TABLE 2. ERG Amplitudes and Statistics

	POAG	Control	Loss (%)	*P*	ROC Area
S-cone a-wave	1.03 ± 0.11	1.40 ± 0.10	26	0.021	0.69
S-cone b-wave	1.57 ± 0.15	2.86 ± 0.32	45	0.001*	0.79
S-cone PhNR	4.24 ± 0.43	6.92 ± 0.52	39	0.0001*	0.86
L&M-cone a-wave	9.99 ± 0.70	12.73 ± 0.88	22	0.021	0.69
L&M-cone b-wave	28.90 ± 1.80	35.68 ± 2.31	19	0.028	0.68
L&M-cone PhNR	30.12 ± 2.01	37.30 ± 1.98	19	0.016	0.73
PERG P50–N95	2.52 ± 0.26	3.65 ± 0.21	31	0.002	0.81
PERG N95	1.14 ± 0.18	1.74 ± 0.17	35	0.02	0.70

Data are expressed as mean microvolts ± SE for ERG amplitudes. Percentage loss relates to mean amplitude reduction in the POAG group. Statistical significance is indicated by *P* (*t*-test), (* highly significant). ROC area is the area enclosed by the ROC curve (chance level = 0.50).

to a pressure-sensitive mechanism. The depressed S-cone b-wave and S-cone PhNR amplitude and the diffuse nature of the damage is consistent with the idea of a pressure-sensitive mechanism affecting the S-cone system selectively. Alternatively, cell losses confined to the ganglion cell layer only and in the arcuate region might be expected to relate to axonal damage at the optic nerve head.[19] It has been reported that a pressure-sensitive reversible reduction in blue sensitivity can be demonstrated in normal subjects,[49] but in this study, the S-cone PhNR reflected permanent damage because these patients with POAG had normal IOPs due to effective treatment (Table 1).

Previous studies have shown that the PERG P50–N95 is highly sensitive to glaucomatous damage[3] and Graham et al.[4] reported that the PERG N95 was the most sensitive parameter in an extensive study of investigative methods. However the study differed from the present one in several respects. The slightly better ROC performance[4] may relate to the fact that the POAG sample had slightly more advanced glaucoma and included six patients with purely diffuse field loss, which should be more easily detected by PERG. In our study the PERG achieved almost as good a performance as the S-cone PhNR. The PERG P50–N95 was statistically significant ($P = 0.002$), and the ROC area score was 0.81, with sensitivity of 72% and specificity of 79%. There is evidence that the amplitude of the PERG is not solely determined by ganglion cell activity. An almost pure ganglion cell signal can be extracted only by a special procedure,[9] which could not be used in clinical studies. The additional sensitivity of the S-cone PhNR may therefore be because the S-cone pathway is more sensitive to glaucomatous damage.

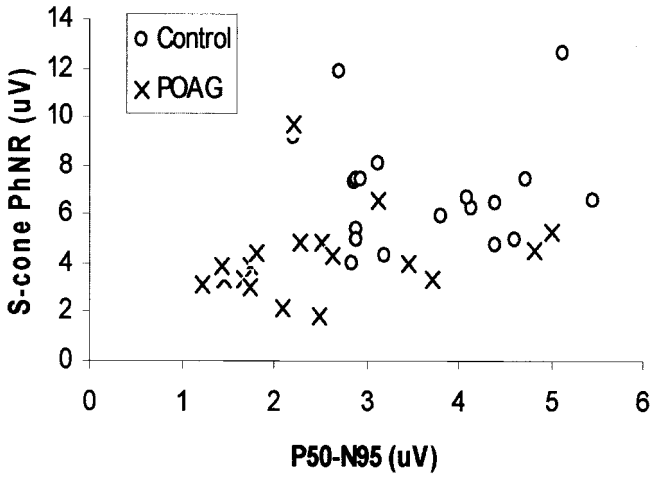

FIGURE 4. Distribution of S-cone PhNR and PERG amplitudes for POAG (*cross*) and control (*circle*) subjects. Means and SE are shown in Table 2. There is only a moderate degree of correlation between the two measures (Spearman's rho $r = 0.50$, $P = 0.032$), indicating their relative independence as diagnostic criteria.

The PERG and the S-cone PhNR may have complementary roles in glaucoma investigation. Although both are sensitive indicators of neural damage, they relate to different pathways and to different areas of the retina. These signals carry separate information that is reflected in their moderate level of correlation in the POAG group, as shown in Figure 4. As in the case of the PERG and perimetry,[5] discrepancies between the test results may be due to different types of neural damage rather than a lack of validity. Because perimetry primarily determined the POAG and control groups, the ERG sensitivities provide persuasive evidence of the potential contribution of electrophysiology to analytical diagnostic procedures.

The L&M-cone PhNR had a lower statistical significance for the reduction in the POAG group and achieved an ROC area score of only 0.73. One reason for this disappointing result may be that the MD was much lower in our patients (−3.22 dB) than in those in the original experimental study (>6 dB),[8] signifying a lower level of diffuse damage in our POAG group that could not be detected so easily. In the recently reported study in patients with POAG in which the L&M-cone PhNR performed well,[13] the MD was again higher (−3.69 dB), signifying slightly more advanced glaucoma, but the test was a focal L&M-cone PhNR confined to the central ganglion cell–rich retina. These comparisons are consistent with the view that the L&M-cone PhNR probably reflects the neural damage over an extended range, whereas the S-cone PhNR is highly sensitive in the earliest stages of glaucoma.

Studies in which SWAP was used demonstrate a reduced response to blue light with increasing age,[18] and there is a widespread belief that media absorption and light scatter must greatly affect any assessment of shortwave sensitivity in older observers. However, surprisingly, in the case of ganzfeld (full-field) stimulation, we have found that this problem is almost absent. Although the wavelength dependence of intraocular scatter is less than that predicted for Rayleigh scattering,[50] red light is nevertheless scattered or absorbed to a substantially lesser extent than blue light.[50] We assumed therefore that the heterochromic flicker match between red and blue would change with age and that a relatively invariant blue stimulus could be determined by a flicker match to a standard red stimulus.

When we attempted to measure the age-related change with the full-field ganzfeld stimulator we found that no statistically significant change could be demonstrated, and a standard level of blue stimulus was adopted for this study in subjects with clear media. We conclude that the age-related effect in SWAP is predominantly due to forward scatter, rather than to absorption. In the case of the perimetric target, the

blue light may be deviated widely by the scattering process, reducing the contrast of the retinal image of the small blue patch. During full-field stimulation however, the effect is quite different, because much of the full-field blue light is simply redistributed on the retina, where it is still effective as a stimulus for flicker photometry or the ERG. The S-cone ERG may therefore be much less affected by age-related changes than is the small stimulus of SWAP. This is consistent with our finding that the S-cone PhNR is not significantly correlated with age in the control group. The strong correlation we observed between S-cone PhNR and the MD of conventional perimetry is a further indication of its potential value in POAG, because MD is the perimetric measure with the best correlation with nerve fiber loss.[51]

Conclusions

Our studies indicate that the S-cone ERG is probably more sensitive than the PERG in early POAG. The S-cone b-wave is significantly affected in POAG, in a manner similar to the S-cone PhNR. It provides evidence of diffuse functional damage to the S-cone bipolar and bistratified midget ganglion cells and other proximal neurons, which are supplied by the retinal circulation, due to a presumed pressure-related mechanism in POAG. This test may provide an opportunity to investigate glaucoma without the variability inherent in psychophysical techniques, including SWAP, and may also be less affected by age-related interindividual variation in intraocular scattered light. The S-cone PhNR is therefore potentially a useful diagnostic signal and should be evaluated on larger and more rigorously constructed samples of patients and control subjects.

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