

Mid-peripheral pattern electrical retinal responses in normals, glaucoma suspects, and glaucoma patients

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Abstract

Aims—Reliance on intraocular pressure, optic nerve cupping changes, nerve fibre layer integrity, and visual field changes may delay treatment of glaucoma since irreversible changes may have already occurred at the time of diagnosis. Abnormal pattern electrical retinal responses (PERR or PERG) have been demonstrated in patients with ocular hypertension (no visual field changes) and glaucoma when visual stimulation was presented to the central field. Since glaucomatous visual field changes tend to occur first in the mid-periphery, the use of PERR outside of the central field may offer an earlier indication of glaucomatous involvement.

Methods—Glaucoma suspects and glaucoma patients were derived from a university practice. Normal subjects were recruited from non-patient volunteers. Alternating bar gratings were presented in the supranasal, supratemporal, infratemporal, and infranasal visual field. Six spatial frequencies, from 0.25 to 6.0 cycles per degree, were used for normal volunteers; three spatial frequencies, from 0.38 to 1.5 cycles per degree, were presented to suspects and glaucoma patients. Time of onset of the first negative (N35) and first positive peak (P50) and the amplitude consisting of the absolute difference between the first negative peak and first positive peak (P50 amplitude) are reported. Age corrected values were determined for normals, suspects, and glaucoma patients for each spatial frequency and for each quadrant in the visual field.

Results—Mean P50 amplitudes from normal subjects showed spatial tuning in all quadrants with reduced low frequency attenuation. Normals demonstrated a small decline in amplitude with age. Glaucoma patients demonstrated an age corrected reduction in amplitude and early implicit times. Glaucoma suspects had values between those of normal and glaucoma subjects. P50 amplitudes were weakly correlated with increasing cup to disc diameter ratio. A glaucoma patient with asymmetric visual field loss demonstrated significant diminution of the PERR bilaterally.

Conclusion—The PERR, using mid-peripheral stimulation, may be a sensitive

tool for the early detection of glaucoma. Further refinements can speed clinical data acquisition and enhance signal to noise ratio.

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Screening patients for glaucoma using a threshold of 21 mm Hg from a single tonometric measurement may overlook up to one half of patients with established glaucomatous optic neuropathy¹ while subjective kinetic or automated static perimetry may indicate the presence of disease only after a significant loss to the retinal ganglion cell layer has already occurred.²⁻³ More objective tests for the early detection of glaucoma currently being studied include peripheral colour contrast testing,⁴⁻⁵ short wavelength automated perimetry,⁶⁻⁷ high pass resolution perimetry,⁶ frequency doubling perimetry,⁸ motion automated perimetry,⁷ the visual evoked potential,⁹⁻¹⁰ and pattern electrical retinal responses (PERR).¹¹⁻¹⁶

The PERR is believed to reflect functioning of the ganglion cells in the inner retina since sectioning of optic nerve results in loss of the PERR on a time course consistent with the death of ganglion cells in the rat,¹⁷ cat,¹⁸ and monkey,¹⁹ and the onset of optic atrophy in humans.²⁰⁻²¹ The PERR, a contrast based system, is potentially useful in the screening of glaucoma suspects since large retinal ganglion cells and their axons projecting to the magnocellular system of the lateral geniculate nucleus appear to be sensitive to contrast stimuli²² and are affected in glaucomatous eyes.²³⁻²⁵ There is evidence that the parvocellular system is affected as well.^{6-7, 24-26} Since mid-peripheral and arcuate scotomas are most often the earliest detectable visual field changes to occur as a result of glaucoma, correlating with the pattern of optic nerve and nerve fibre layer damage,²⁷⁻²⁸ a protocol was sought to test the mid-peripheral retina at least 4° from central fixation.

Methods

Nineteen subjects (24 normal eyes), aged 16 to 77 years (mean 33.5 (SD 14.1)) were recruited for this study. Best corrected visual acuity was 20/20. Ophthalmological examination was normal, as was testing with Farnsworth-Munsell 15 hue tiles and with American Optical contrast sensitivity plates. Seven glaucoma suspects (14 eyes) aged 37-61 years (48.1 (8.53)) were examined. Visual acuity was 20/20 in both eyes and automated (Humphrey) visual fields exhibited no pattern defects.

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Table 1 Clinical characteristics of seven glaucoma suspects during study

	Subject						
	1	2	3	4	5	6	7
C/D (RE)	0.3	0.3	0.3	0.3	0.7	0.2	0.3
C/D (LE)	0.6	0.5	0.3	0.3	0.7	0.1	0.6
Peak IOP (RE)	26	30	26	30	28	33	31
Peak IOP (LE)	22	24	26	26	27	33	30
Medication	DPH	BB	None	BB	BB	BB	None

C/D = clinical cup to disc diameter ratio; DPH = dipivefrin hydrochloride; BB = topical β blocker.

Suspects fulfilled one of three criteria: a cup to disc diameter ratio (C/D) of 0.6 or greater in either eye, C/D asymmetry equal to or greater than 0.2 between eyes, or intraocular pressure (IOP) of 26 or greater at the time of screening examination (Table 1). C/D was determined in suspects and glaucoma patients clinically by one of us (MBS).

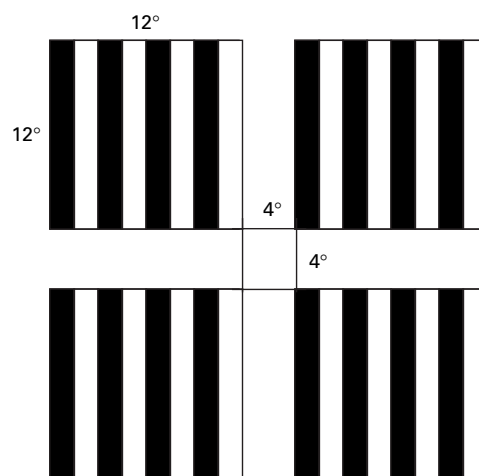


Figure 1 Representation of pattern stimulation to the retina. In actuality, one video monitor was used while the subject fixated on targets around the display.

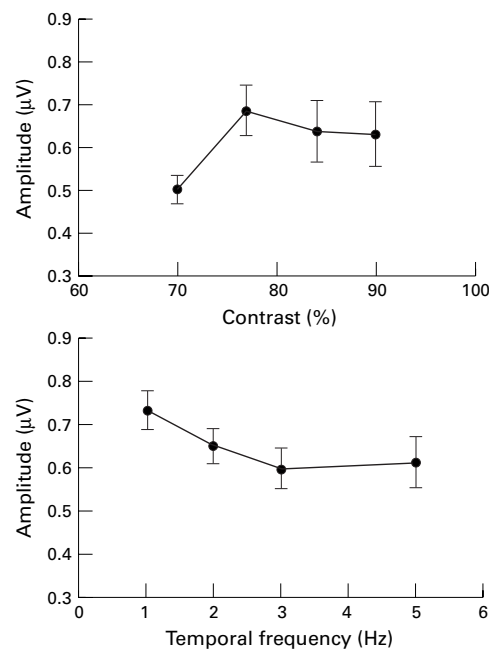


Figure 2 Mean of P50 amplitudes in a pilot study of four subjects in all four quadrants tested at a spatial frequency of 0.75 cpd and a temporal frequency of 3 Hz (above) and 77% contrast (below).

Table 2 Mean pupil sizes for each of the three study groups

Group	Mean pupil size (mm)	SD
Normal	2.7	0.67
Suspects	2.4	0.79
Glaucoma	2.6	0.85

Nine subjects (18 eyes) with definite glaucomatous visual field loss aged 50–74 (mean 62.8 (SD 8.64)) but with no media opacities or retinal abnormalities were studied. Humphrey visual field analysis revealed a primary superior or inferior arcuate loss in six eyes, both superior and inferior loss in four eyes, nasal loss in four eyes, mid-peripheral defects in one eye, and minimal pattern loss in three eyes (fellows of more severely affected eyes). Visual acuity was 20/25 in all but three eyes (20/50) of three patients, as a result of advanced glaucoma. Spectacle correction was used during testing. Potential subjects with diabetes mellitus, uncontrolled hypertension, or any retinal abnormality were excluded. Informed consent was obtained for all subjects following approval of the project by the University of Florida Health Sciences Institutional Review Board.

During the pilot phase of the study, the PERR and visual evoked potential (VEP) of four eyes from four normal subjects, aged 22–43 were obtained using contrasts of

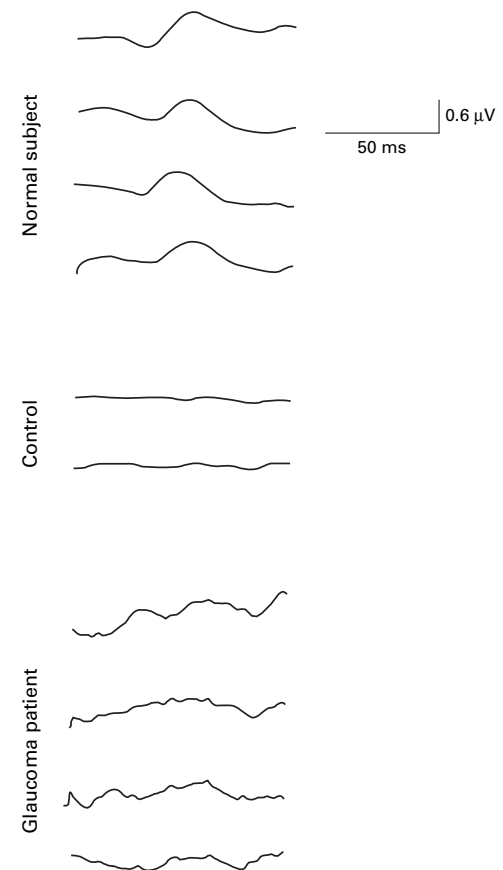


Figure 3 Actual PERR of four consecutive averages in a normal subject (0.75 cpd) (top), two control acquisitions from the same subject obtained with a non-alternating pattern (middle), and four repeated measures from a patient with glaucoma (0.75 cpd) (bottom). Calibration bars for amplitude and time are shown.

Table 3 Mean amplitude (μV) in normal subjects for each spatial frequency by quadrant

	Spatial frequency (cpd*)					
	0.25	0.38	0.75	1.5	3	6
Supranasal	0.534	0.623	0.700	0.634	0.536	0.275
Supratemporal	0.555	0.597	0.603	0.566	0.446	0.314
Infratemporal	0.743	0.610	0.712	0.736	0.596	0.356
Infranasal	0.690	0.666	0.751	0.657	0.449	0.400

*Cycles per degree.

70–90% and temporal frequencies of 1–5 Hz at a constant spatial frequency of 0.75 cycles per degree (cpd). For the main phase of the study, bar sizes of 5, 10, 20, 40, 80 and 120 min of arc (6.0–0.25 cpd) were presented to normals at 6.4 reversals per second (3.2 Hz) and 77% contrast ($(L_{\max} - L_{\min}) / (L_{\max} + L_{\min})$). The reversing square wave bar patterns were presented at 1 metre on an Electrohome high resolution monochrome monitor. Pupil sizes were recorded. Glaucoma subjects and suspects were presented bar sizes of 20, 40, and 80 min of arc (1.5, 0.75, and 0.38 cpd), spatial frequencies where amplitudes in normal subjects were greatest: 100–200 samples of 250 ms duration produced an averaged signal. Four measures were taken for each quadrant and spatial frequency using the Nicolet Med 80 computer and averaged for each eye. The computer and analogue to digital converter were capable of 20 bit accuracy. Signals were bandpass filtered between 0.02 and 58 Hz. A 60 Hz notch filter was employed. Artefact rejection was used to exclude signals exceeding plus or minus 75 μV . A total stimulus size of $12^\circ \times 12^\circ$ was presented in each of the four quadrants in the visual field—the supranasal, supratemporal, infranasal, and infratemporal quadrants. The centre of each stimulus field was located 11.3° from

fixation. The mean luminance of the stimulus was 46 cd/m^2 ; the background luminance, produced from low voltage floodlights with diffusers illuminating a white matt background, was 34 cd/m^2 . Control samples were measured using a non-alternating pattern and again with a blank screen of the same mean luminance as that of the patterns.

Subjects were seated in an electrically shielded room and directed to fixate on numbered targets providing the eccentric fixation necessary for stimulation in the oblique quadrants (Fig 1). A headrest was used to support the occiput. Proxymetacaine (proparacaine) was instilled into the eyes. Acquisition was stopped every 7–10 seconds whereupon the patient was instructed to blink. Recording occurred only when stability of baseline was present. Retinal potentials were recorded using a DTL electrode²⁹ placed in the tear lake of the lower eyelid; reference and ground Ag/AgCl electrodes were placed on the ipsilateral outer canthus and on the midline forehead, respectively. The DTL lead was taped into place on the lower lid. Fixation was monitored with a video camera and monitor. Subjects who had difficulty maintaining fixation were asked to train the spot of a hand held laser pointer on the fixation target. This technique resulted in stable fixation in all subjects.

The P50 amplitude was measured from the nadir of the first negative peak (N35) to the zenith of the first positive peak (P50); the N95 amplitude was measured from the P50 peak to the second negative peak (N95). Implicit time was measured from the onset of the trigger to N35 and P50. N35 peaks were measured when present between 31 and 50 ms and P50 peaks

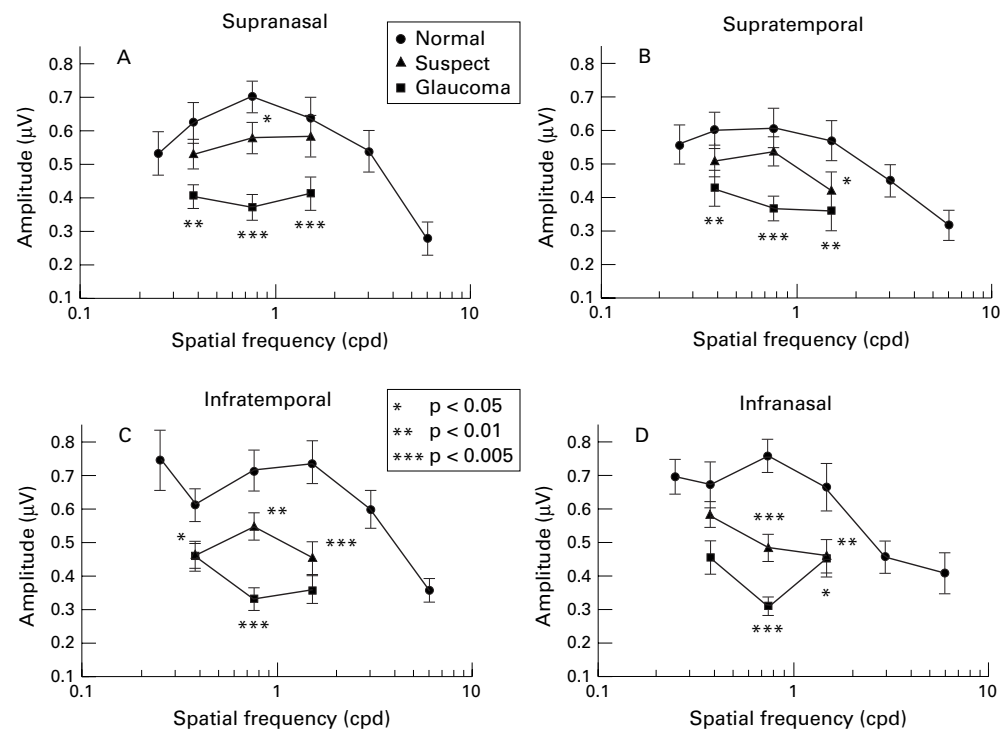


Figure 4 Mean P50 amplitudes for normals, glaucoma suspects, and glaucoma patients by quadrant. *p* Values pertain to comparisons between normals and either glaucoma suspects or patients. Bars represent standard error of the mean.

Table 4 Age adjusted P50 amplitudes (0.75 cpd) for each group by quadrant

	Normal	Suspect	Glaucoma
Mean (μV)	0.630	Infratemporal 0.547	0.344
p Value		0.362	0.001
Mean (μV)	0.669	Infranasal 0.486	0.314
p Value		0.031	<0.001
Mean (μV)	0.521	Supratemporal 0.429	0.342
p Value		0.334	0.021
Mean (μV)	0.618	Supranasal 0.546	0.297
p Value		0.441	<0.001

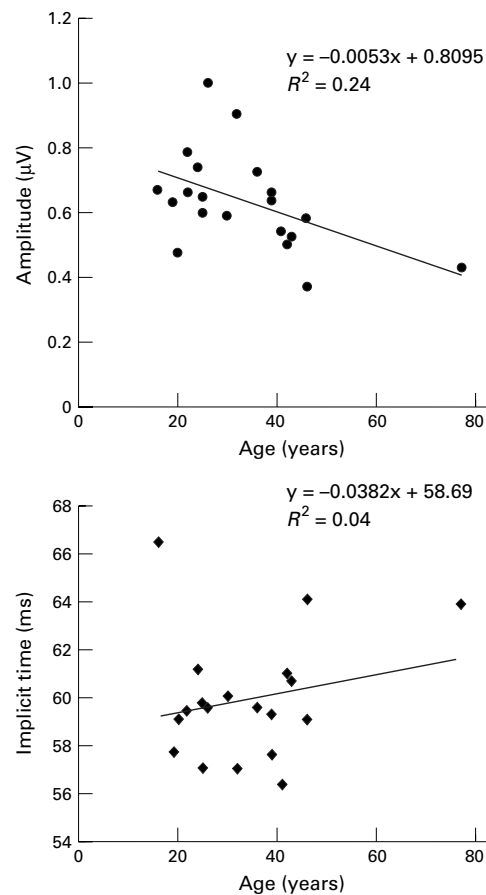


Figure 5 Mean P50 amplitudes (above) and P50 implicit time (below) for normals averaged for all quadrants and compared with subject age.

were similarly measured when present between 45 and 65 ms. Background noise level was measured as the average peak to peak amplitude during presentation of the non-alternating control stimulus. Mean amplitudes measured during actual stimulation that fell below this level were labelled as non-detectable.

The VEP was initially recorded simultaneously with the PERR using monocular stimulation in normal subjects. VEP recording was halted early in the main phase of the study in favour of binocular acquisition of the PERR after analysis yielded an unacceptably high intrasubject variability of the cortical signals.

Student's *t* test was used to compare amplitudes and implicit times between subject groups. Analysis of variance (ANOVA) was

used to test for differences between quadrants within each subject group ($\alpha = 0.05$). Linear regression analysis was performed on comparisons of the P50 amplitude and implicit time with age and C/D.

Results

In the pilot phase of the project, maximal P50 amplitudes of the PERR were achieved using a pattern of 77% contrast (Fig 2). Lower temporal frequencies produced stronger signals. In the main phase of the study ANOVA showed no significant difference between mean pupil sizes of the study groups ($p=0.62$) (Table 2). Figure 3 depicts four consecutive measures of a normal subject using the 0.75 cpd (40 min of arc) pattern, two control acquisitions from the same subject and four repeated measures from a patient with glaucoma (0.75 cpd). The N35 and P50 components were reproducible throughout the trial whereas the N95 component was subject to significant variability and excluded from final analysis.

P50 amplitudes in normal subjects are maximal at 0.75 cpd in all quadrants except infratemporally where the greatest amplitudes are produced using the 0.25 cpd grating (Fig 4). There is a trend of decreasing amplitude as larger or smaller gratings are used. The largest grating (0.25 cpd) controverts this trend, however, in the inferior quadrants. Presentation to the lower quadrants (Fig 4C, D) produced signals of greater amplitude than in the superior quadrants (Fig 4A, B) (Table 3). Stimulation of the supratemporal visual field produced the lowest signals. For each spatial frequency, however, a significant difference could not be demonstrated between quadrants (ANOVA).

Glaucoma suspects showed significantly lower amplitudes compared with normals at 1.5 cpd in the supratemporal ($p<0.05$), infratemporal ($p<0.005$), and infranasal ($p<0.01$), quadrants (Fig 4). At 0.75 cpd, lower amplitudes were observed in the supranasal ($p<0.05$), infratemporal ($p<0.01$), and infranasal ($p<0.005$) quadrants. At 0.38 cpd, a significantly lower amplitude was noted only in the infratemporal quadrant ($p<0.05$).

Glaucoma patients demonstrated lower amplitudes compared with normals in all quadrants at 1.5 cpd (supranasal ($p<0.005$), supratemporal ($p<0.01$), infratemporal ($p<0.005$), and infranasal ($p<0.05$)), 0.75 cpd ($p<0.005$ in all quadrants) and for the 0.38 cpd stimulus ($p<0.01$ in the superior quadrants; $p<0.05$ in the inferior quadrants). The smallest amplitudes were produced at 0.75 cpd in three of four quadrants.

Regression analysis comparing mean amplitudes for normals averaged for all quadrants versus subject age showed a decrease in amplitude of 0.053 μV per decade as depicted in Figure 5 ($R^2=0.24$; $p=0.03$). The slope of the regression curve was used to normalise P50 amplitudes for each of the averaged acquisitions for normals, glaucoma suspects, and patients to an arbitrary standard age of 50 years (Table 4). This resulted in an average adjustment of 12% in the amplitudes. *t* Test comparison indicated that there was a

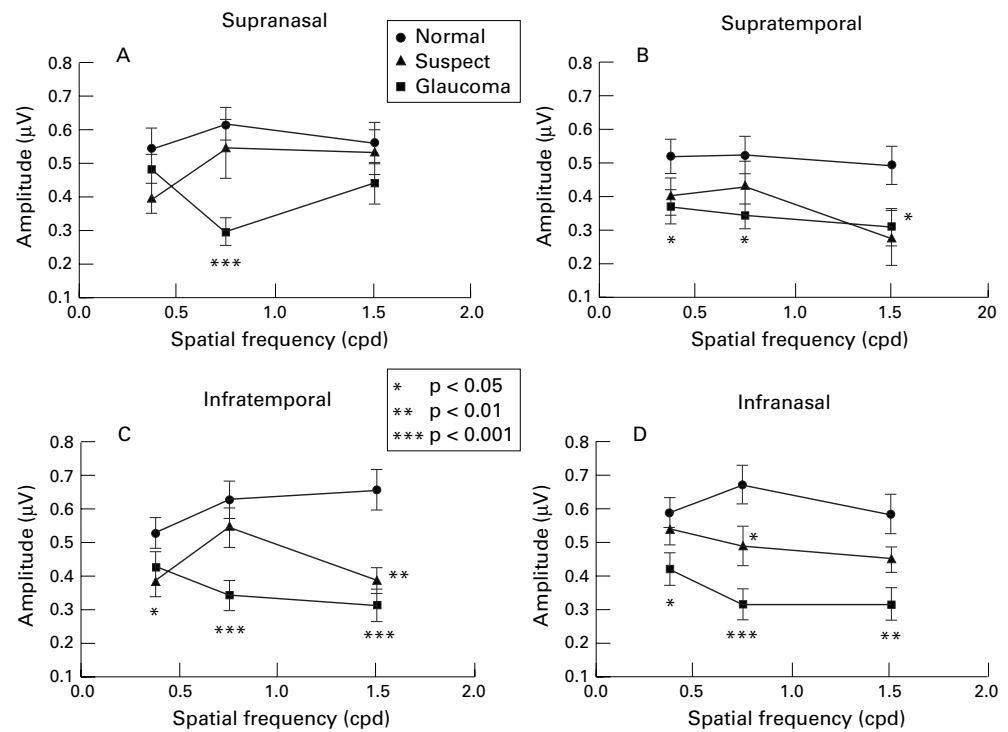


Figure 6 Age corrected mean P50 amplitudes for each group by quadrant. *p* Values pertain to comparisons between normals and either glaucoma suspects or patients. Bars represent standard error of the mean.

significant age corrected difference between normals and suspects in the infratemporal quadrant ($p < 0.05$) using the 0.38 cpd grating, in the infranasal quadrant ($p < 0.05$) using the 0.75 cpd grating, and in the infratemporal quadrant ($p < 0.01$) using the 1.5 cpd pattern

(Fig 6). Glaucoma patients demonstrated a significant age corrected reduction in P50 amplitude in the supratemporal and infranasal quadrants ($p < 0.05$) using the 0.38 cpd grating, in all quadrants using the 0.75 cpd grating ($p < 0.001$ except supratemporally, $p < 0.05$),

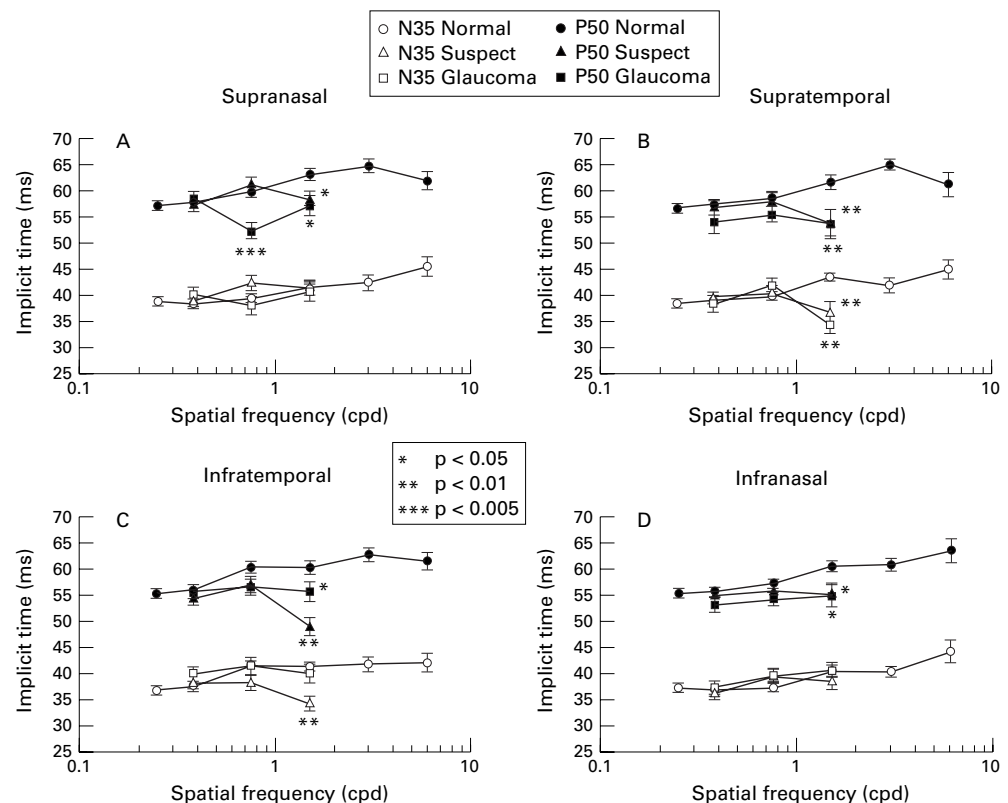


Figure 7 Implicit time (N35, P50) for each group by quadrant. *p* Values pertain to comparisons between normals and either glaucoma suspects or patients. Bars represent standard error of the mean.

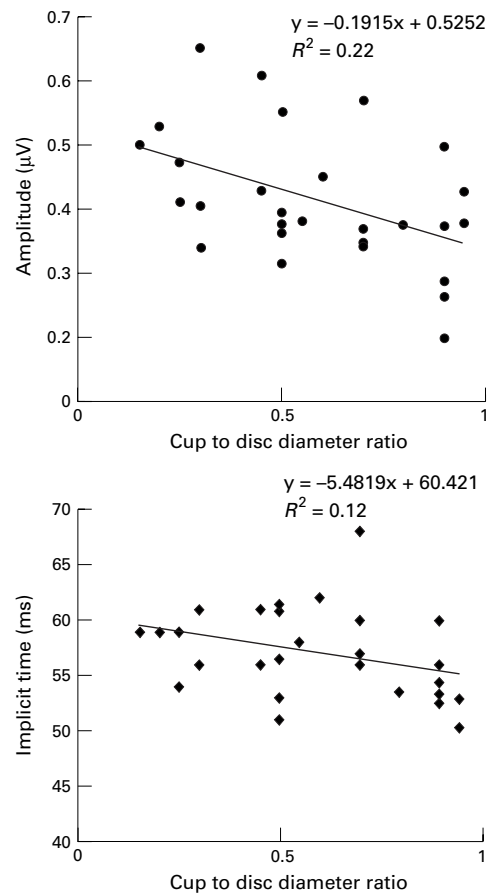


Figure 8 Mean P50 amplitudes (above) and P50 implicit time (below) for glaucoma suspects and patients averaged for all quadrants and compared with cup to disc diameter ratio.

and in 3 quadrants using the 1.5 cpd grating (supratemporal $p < 0.05$, infratemporal $p < 0.001$, infranasal $p < 0.01$).

The average implicit time of the first positive peak in normals was 60 ms (95% confidence interval (CI) = 59.5–60.5). There was no significant difference in implicit times (N35 or P50) between quadrants in normal subjects at any spatial frequency tested (Fig 7). In glaucoma suspects, earlier onset of P50 was noted at 1.5 cpd in the temporal quadrants ($p < 0.01$) and nasal quadrants ($p < 0.05$), while earlier onset of N35 was noted only in the temporal quadrants ($p < 0.01$). Glaucoma patients demonstrated earlier onset of P50 in each quadrant at 1.5 cpd ($p < 0.05$, except the supratemporal quadrant $p < 0.01$). Earlier onset of N35 at this spatial frequency in patients was noted only in the supratemporal quadrant ($p < 0.01$). Early onset of P50 using the 0.75 cpd pattern is significant only in the supranasal quadrant ($p < 0.005$) in glaucoma patients. Regression analysis of implicit times in normals *v* subject age (Fig 5) revealed an increase in implicit time of 0.38 ms per decade which was not significant ($R^2 = 0.04$; $p = 0.39$).

Cup to disc diameter ratios (C/D) of glaucoma suspects and patients were compared with each subject's age corrected mean P50 amplitudes and implicit times (Fig 8). Increasing C/D was correlated with decreasing

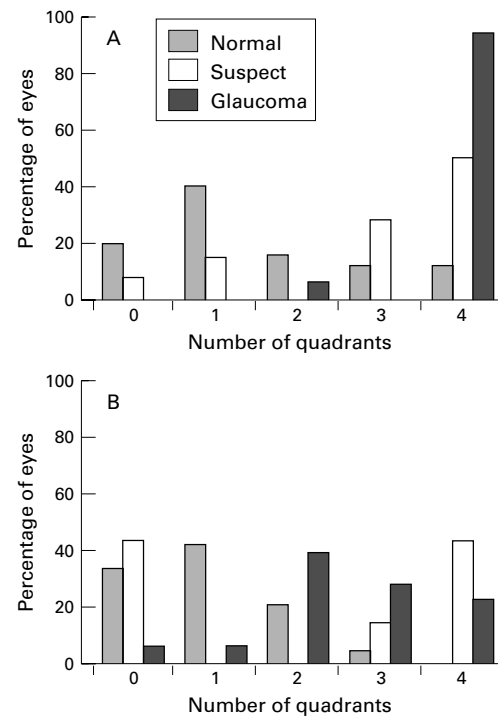


Figure 9 Quadrant error: number of quadrants outside 95% confidence limits for P50 amplitude (0.75 cpd) (A) and P50 implicit time (1.5 cpd) (B).

amplitude with a $R^2 = 0.22$ ($p = 0.01$) and to earlier implicit times with a $R^2 = 0.12$ ($p = 0.07$).

Waveforms were compared between groups using non-alternating patterns as controls. Normal subjects had the highest signal to noise ratio (3:1); suspects had a lower ratio (2.5:1) and glaucoma patients had the lowest (1.5:1). This is consistent with the overall smaller signals produced by glaucoma patients. Identifiable waveforms were obtained in 99% of signals produced by normals, 89% by suspects and in 80% of signals by glaucoma patients.

Ninety five per cent confidence intervals were determined for amplitude and implicit time (P50) measurements derived from normative data using 0.75 cpd and 1.5 cpd spatial frequencies respectively. The number of quadrants with amplitudes or implicit times falling out of the 95% CI were determined (Fig 9). Seventeen glaucomatous eyes (94%) had all four quadrants with abnormal amplitudes. Seven suspect eyes (50%) and three normal eyes (13%) were similarly out of range. Of the subject eyes with P50 implicit times out of the 95% CI in three or four quadrants, one (6%) was a normal eye, eight (44%) were suspects, and nine (50%) were glaucoma patients. Using the following criteria—a mean P50 amplitude (0.75 cpd) falling outside of the CI in more than two quadrants and an implicit time (1.5 cpd) falling outside of the CI in more than one quadrant—an accurate prediction of glaucoma would occur with 96% specificity, 88% sensitivity, and a 94% predictive value.

One patient with primary open angle glaucoma and asymmetric visual field loss was found to have no detectable signal characteristics in three of four quadrants in the affected eye (Fig 10). The remaining quadrant

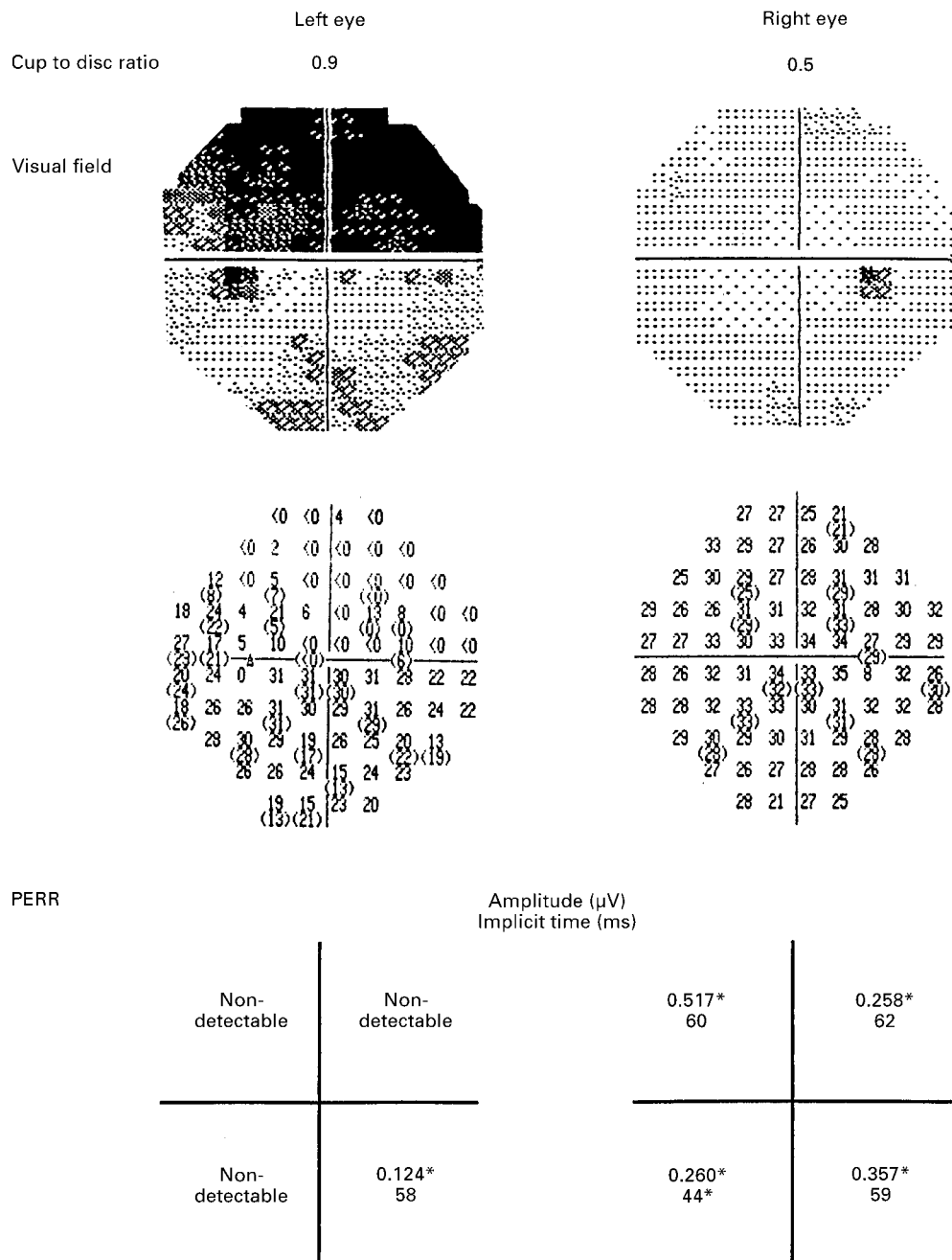


Figure 10 Patient with glaucoma affecting eyes asymmetrically. Humphrey visual field using 30-2 program is represented. Lower portion of figure represents mean P50 amplitude (0.75 cpd) and P50 implicit time (1.5 cpd) in each tested quadrant. *Indicates value outside of the 95% confidence interval.

produced a P50 amplitude that was 19% (>2 SD) of the age corrected value for that quadrant. Humphrey testing showed two loci out of 37 that were outside of age adjusted normal values with a $p < 0.5\%$. The fellow eye, with an apparently normal visual field, was found to have PERR amplitudes outside of the 95% confidence interval in all four quadrants.

Discussion

Previous reports have shown a reduction in the PERR in glaucoma patients or ocular hypertensives using central stimulation.^{11-16 30} There is evidence that the optic nerve² and nerve fibre layer²⁷ are damaged in a selective manner yielding mid-peripheral and paracentral visual

field defects. Since the population of ganglion cell types varies with retinal location—a proportionately higher number of smaller cells within the central 4° but larger cells more peripherally³—we wanted to exclude central ganglion cells from contribution to the PERR and focus on cells which may be more susceptible to early glaucomatous damage. The stimulus was thus presented by quadrants.

Overall, signals in normals were small—between 1/2 µV and 3/4 µV, which is consistent with the observation that with increasing eccentricity there is a decrease in the total ganglion cell density^{25 31} and a gradual decrease in the PERR amplitude.³² Owing to the nature of the small signals, the N95 amplitude of the

PERR was not included in the final analysis because of high intraindividual variability.³³ The efficacy of the P50 amplitude in the testing of glaucoma patients and suspects has been observed previously.³⁴⁻³⁷

Attenuation of P50 amplitudes in normals which is observed at lower and higher spatial frequencies is reminiscent of the spatial tuning pattern seen using central stimulation.³⁸⁻⁴¹ Tuning has been previously noted using mid-peripheral stimulation as well, with a peak response at approximately 60 min of arc (0.5 cpd).³²⁻⁴¹ Maximal amplitudes were evident in the normal subjects under current study using gratings of 0.75 cpd. Tuning has been ascribed to optimal pairing of stimulus to receptive field characteristics.⁴¹ A spatial tuning curve may also reflect reduced responses at higher spatial frequencies where there is diminished contrast of the retinal image from inherent limitations of the optics of the eye.⁴⁰ Attenuation of signal at relatively low spatial frequencies (using smaller stimulus fields as in this study) may be due to lateral inhibitions of receptive fields by ganglion cells. Low spatial frequency attenuation (LSFA) is not as readily apparent in the normal subjects under current study. While higher stimulus luminances than that used in this trial have been implicated in increased local luminance responses and loss of LSFA,³⁸ the less observed LSFA in this study may result from a shift in relative receptive field sizes in the mid-periphery and has been observed before.³²⁻⁴¹

The decline of P50 amplitudes with age is consistent with a reduction in retinal ganglion cells outside of the fovea when specimens of younger patients were compared with those of the more elderly.⁴² Repka and Quigley found no significant age related decline in total axon number, but did observe a diminishment in mean fibre diameter with age.⁴³ Other studies have shown conflicting evidence of the effect of age on the optic nerve using imaging⁴⁴⁻⁴⁵ or histological⁴⁶ techniques. There is more consistent agreement, however, on a reduction in the pattern electrical response of older eyes.¹⁵⁻¹⁶⁻³³⁻⁴⁷⁻⁴⁸ The differential effect of age in the three current study groups was mitigated by normalising the P50 amplitudes for each subject based on age. Using this correction, statistically significant differences were present between normals and glaucoma patients using the 0.75 cpd grating, the spatial frequency where P50 amplitudes were generally the greatest in normal eyes and the smallest in glaucomatous eyes. Glaucoma suspects had values intermediate to normals and patients which were generally not shown to be statistically significant. This may reflect a heterogeneous sample in this group representing subjects with normal eyes and those with possible damage from early glaucoma before developing Humphrey visual field loss.

The early onset of P50 in glaucoma suspects and patients is statistically significant and is consistent throughout the four quadrants at the 1.5 cpd spatial frequency. Early implicit times have not been previously reported using central stimulation but have rather been

observed to be unchanged³⁴⁻³⁷ or prolonged.³⁵⁻³⁶⁻⁴⁹ There is evidence that both magnocellular²³⁻²⁵ and parvocellular⁶⁻⁷⁻²⁴⁻²⁶ systems are affected in glaucoma but the proportion of M and P cells change with retinal location³ as does their relative electrical contribution.⁵⁰ Further study of the PERR in the mid-periphery is necessary to establish the consistency of this observation.

The association between C/D and implicit time is too weak to firmly correlate earlier onset with increasing C/D. A slightly stronger correlation was found between C/D and amplitudes in glaucoma suspects and patients and has been investigated previously showing support⁴⁷⁻⁴⁹ and lack thereof⁵¹ for such a relation.

In one patient with highly asymmetric primary open angle glaucoma, the PERR was relatively more sensitive than Humphrey visual field testing in the affected eye. Though previous reports have shown abnormalities in the PERR before progressive cupping of the optic nerve³⁵ and in the uninvolved fellow eyes of patients with glaucoma,¹¹ only longitudinal follow up will demonstrate the predictive value of the PERR in this and similar patients.

In our patient population, the mid-peripheral PERR using quadrantal presentation is characterised by spatial tuning, reduced low spatial frequency attenuation, and susceptibility to damage from glaucoma with lower P50 amplitudes and earlier implicit times. This method may provide an additional sensitive means for detecting damage to the inner retina. Larger sampling and sequential testing during glaucoma progression are needed to firmly establish validity of this system.

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