Spatial and Temporal Frequency Tuning of Pattern-Reversal Retinal Potentials (PRRPs)

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Abstract

Bloom and Sokol, Feb. 1977; Armington, Corwin, and Marsetta, Nov. 1971; and Maffei and Fiorentini, Feb. 1981; have described in detail electroretinographic responses evoked by spatially oscillating checkerboard patterns. Maffei and Fiorentini proposed that this pattern-reversal ERG may provide a new diagnostic tool for early detection of diseases specific to the ganglion cells and optic nerve. Evidence obtained from sectioning the optic nerves of cats suggests that the electrical response observed from patterned stimuli arises primarily from the ganglion cells of the retina. Diffuse Flash Electroretinograms, presently used in electrodiagnostic evaluation of retinal pathology have their primary etiology in the photoreceptor and the inner nuclear layers of the sensory retina. These tests are not effective in diagnosing pathology arising in subsequent layers of the visual pathway. Although VER's may be of diagnostic value for optic nerve and cortical evaluation, no present electrodiagnostic test can explicitly evaluate ganglion cell defects. It is the intention of this project to examine pattern-reversal retinal potentials to obtain normative clinical data using different temporal and spatial frequency patterns to determine appropriate parameters to obtain the most reliable responses. Subsequent application of this data to patients with optic nerve disease will also be examined.

The use of phase alternating patterns to evoke electrical potentials from the human retina is not a novel concept. Riggs and his colleagues (Johnson and Schick)[1,2] described retinal potentials obtained with phase reversing gratings and demonstrated that these potentials primarily reflect photopic activity. The photopic nature of these "pattern-reversal retinal potentials" was further confirmed by investigations into the influence of luminance, spatial frequency and wavelength on the characteristics of the response.[3,4] Since pattern-reversal potentials (PRRPs) primarily reflect photopic activity, some authors have suggested that these potentials may provide a method for clinical evaluation of macular function.[5,6]

Pattern-reversal retinal potentials are different from conventional electroretinograms in that they are electrical retinal responses evoked from the human retina by an alternating black and white checkerboard pattern. (Figure 4) This stimulus is used in place of the conventional Ganzfield flash or flicker type of stimulus used with normal ERG testing.[16] (Figure 5) An electrode arrangement, amplification and signal averaging process, similar to that used in obtaining conventional ERGs, is employed in the PRRP technique. (Figures 3 and 6) When comparing the PRRP and conventional ERG,

one finds a marked reduction in PRRP amplitude. Since these responses are so small in amplitude (one to five microvolts) sophisticated electronic equipment is required to obtain reliable responses. Furthermore, the typical electrodes used for clinical electroretinography[7,8] often cause optical blur which can substantially reduce the amplitude of the pattern-reversal response.[6,9] Therefore, other techniques for macular electroretinography such as VERs are more frequently employed.[10]

Renewed interest in the PRRP was generated by a recent report that cats, which initially exhibited normal PRRPs, exhibited sub-normal responses following optic nerve section.[11] The authors assumed a retrograde ganglion cell degeneration took place following surgical sectioning of the optic nerve. The authors contend that this result suggests that, unlike the flash ERG which is indicative of electrical activity from the photoreceptors and inner nuclear layer, PRRPs represent ganglion cell activity. Therefore, the PRRP may be useful in localizing retinal lesions primarily affecting the processing of macular information within the ganglion cell layer. If this is the case, then PRRPs would complement flash and flicker electroretinography providing a method for layer-by-layer analysis of retinal integrity. This theory is further supported by research which showed a similar reduction in PRRP amplitude with normal flash and flicker ERG responses

in patients with chronic monocular glaucoma and unilateral optic atrophy. If this phenomenon is further verified in future research studies, the utilization of this technique may be of diagnostic value in patients with glaucoma, optic atrophy, or especially retrobulbar neuritis or other optic nerve diseases where no funduscopic changes can be seen.

At present, little is known concerning the stimulus specificity of normal human PRRPs. It is clear that these retinal potentials exhibit a spectral sensitivity comparable to the human photopic luminosity function.[2] It is also evident that the amplitude of the PRRP increases to a saturated level over the photopic range of luminances.[3] Additionally, Armington and his colleagues were able to demonstrate that the amplitude of the PRRP decreased with increasing spatial frequency. However, since no determination of optical clarity or subjective visual acuity were included, conclusions concerning spatial frequency dependent relationships were somewhat limited.

The present experiment was designed to systematically examine the effect of variations in temporal and spatial frequency on normal human PRRPs. We find that both spatial and temporal frequency influence the amplitude of the averaged PRRP. As an extension, we find that under appropriate stimulus conditions, the averaged PRRP may predict subjective visual acuity. This presents another potential clinical value for the PRRP technique.

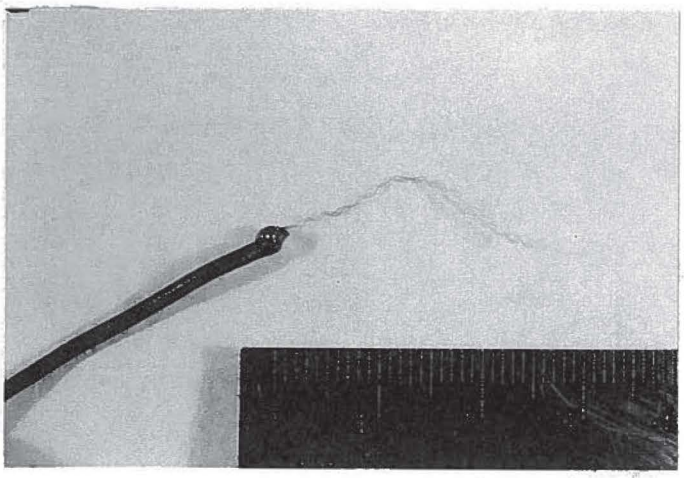

Figure 1

D.T.L. Fiber Electrode

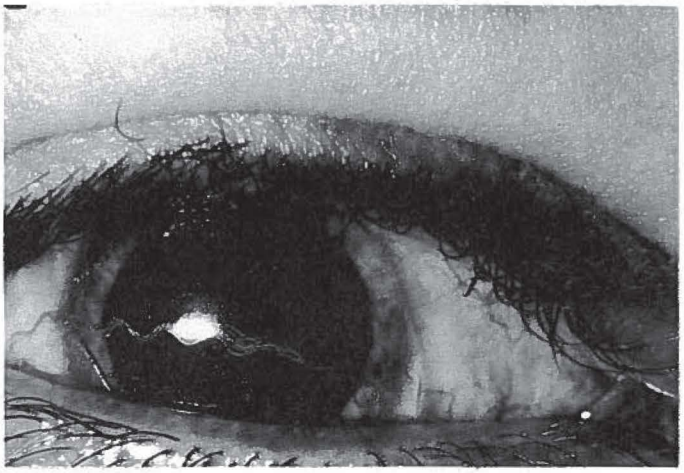

Figure 2

D.T.L. Fiber Electrode placed across subject's corneal apex, secured in position with a hydrophillic contact lens.

Methods and Materials

Fourteen visually normal subjects, ranging from 20 to 31 years of age and selected from the faculty and student body of the Ferris State College of Optometry, were examined. All subjects were emmetropic or corrected to emmetropia and assumed to be free of ocular pathology. For each subject either the right or the left eye was tested.

A DTL fiber electrode,[12] (Figure 1) placed across the corneal apex and secured in position with a plano-power hydrophillic contact lens, was used to record PRRPs. (Figure 2) A Ag-AgCl electrode attached with electroconductive paste near the temporal canthus served as a reference, while

a similar electrode attached to the subject's forehead was used as a ground. (Figure 6a) Visual acuity was measured both with and without the electrode-contact lens combination in place. With the electrode-contact lens combination in place, visual acuity was often slightly reduced, but the reduction was rarely more than one Snellen line.

The PRRPs obtained with this electrode arrangement were differentially amplifed ($x10^4$), bandpass filtered (1-35 Hz, -3 db points) and recorded on a Nicolet CA-1000 signal averaging computer. (Figure 3) Each PRRP was recorded for a 120 msec epoch, and 100 stimulus repetitions were averaged. (Table I)

The black and white checkerboard stimulus was generated on a television monitor using a Nicolet 1006 Visual Stimulator. (Figure 4) The checkerboard pattern filled the entire screen of the monitor, and subtended a visual angle of 12.6° x 16.4°. Each subject viewed the stimulus at a distance of one meter and was directed to fixate a black spot in the center of the television monitor, while keeping the checkerboard pattern in focus. (Figure 4) The contrast of the checkerboard array was set at 74% with a space-averaged luminance of 26 cd/m^2. For each subject, 30 randomly ordered stimulus conditions, representing all possible combinations of six square-wave modulated spatial frequencies (ranging from 0.125 to 4.00 cycles/degree) and five square-wave modulated temporal frequencies (ranging from 0.94 to 15.00 Hz) were tested. (Table II) A condition in which the TV stimulator was tuned to visual noise was also included in each session.

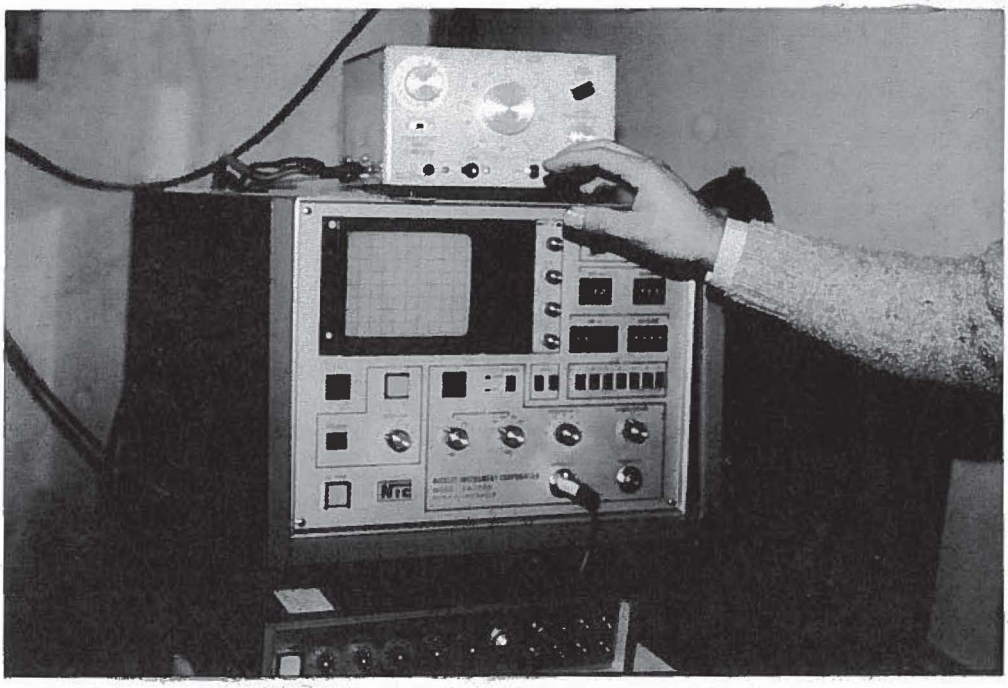

Figure 3

Nicolet CA-1000 Signal Averaging Computer used in recording averaged PRRPs.

Figure 4

Subject viewing checkerboard stimulus at 1 meter viewing distance.

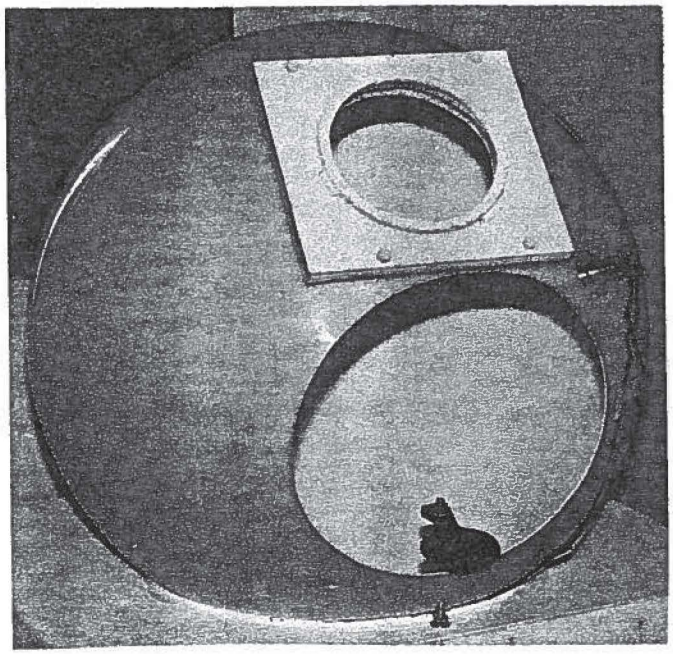

Figure 5

Ganzfield stimulus apparatus for conventional ERG stimulus presentation.

Figure 6

Electrode placement in typical PRRP recording.

RECORDING PARAMETERS

(NICOLET CA-1000)

ELECTRODES - ACTIVE (CORNEA)	DTL FIBER
REFERENCE (TEMPORAL CANTHUS)	Ag-AgCl
GROUND (FOREHEAD)	Ag-AgCl
AMPLIFICATION (DIFFERENTIAL)	10^4
FILTER (BANDPASS)	1-35 Hz
NUMBER OF AVERAGES	100
AVERAGING EPOCH	120 msec

Table I

STIMULUS PARAMETERS

(BLACK AND WHITE CHECKERBOARD ARRAY)

SPACE-AVERAGED LUMINANCE	26 cd/m^2
CONTRAST	74%
FIELD SIZE	12.6° x 16.4°
SPATIAL FREQUENCY (Square-wave modulated)	0.125 to 4.0 cycles/degree
TEMPORAL FREQUENCY (Square-wave modulated)	0.94 to 15.0 Hz

Table II

Results

Reliable PRRPs could be obtained for all stimulus conditions. Despite the very small response amplitudes obtained, a consistent response-to-noise ratio of approximately 6:1 was evident throughout the experiment. The typical averaged PRRP was a biphasic waveform with an initial negative potential followed by a larger positive potential. (Figure 7) Occasionally, the initial negative limb was substantially diminished leaving only a slight "shoulder" preceding the positive potential. In these cases the most negative portion of this "shoulder" was considered to be the trough of the negative potential. Otherwise, the PRRP waveform was quite similar to those depicted elsewhere (Sokol and Nadler, 1979).

For each stimulus condition PRRP amplitude, defined as the difference in voltage between the most negative portion of the initial negative deflection and the most positive portion of the following positive deflection, was determined. PRRP latency, taken as the time difference between the stimulus alternation and the peak of the positive potential, was also measured and found to be consistently between 50-60 msec. Since no substantial variation in PRRP latency was observed, only PRRP amplitude will be considered in the discussion which follows.

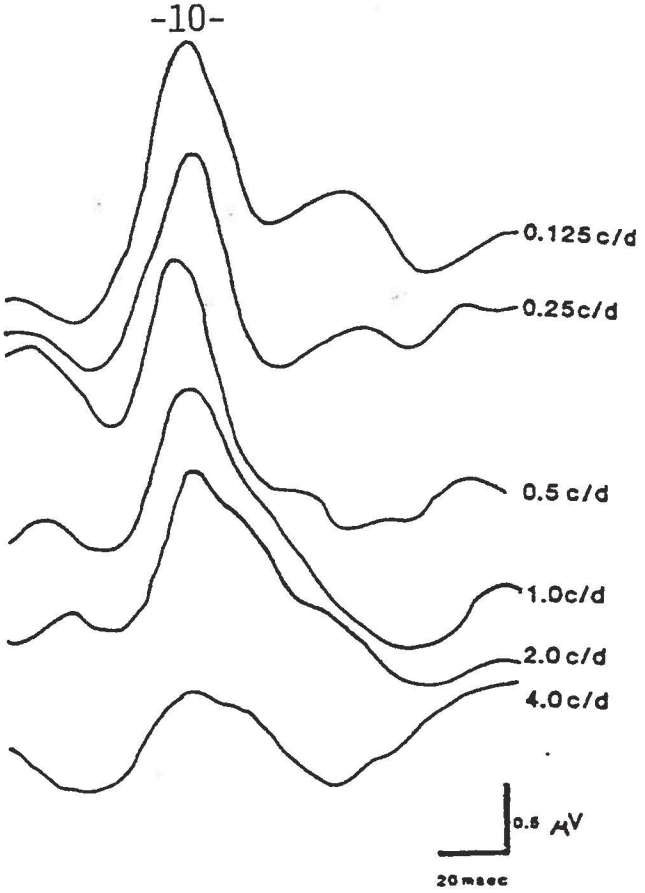

Figure 7

A series of PRRPs elicited from a typical subject. The temporal frequency was 3.75 Hz and the spatial frequency is denoted to the right of each PRRP.

During the course of this experiment, it was noted that the data obtained with the largest check size (0.125 c/d) was considerably more variable than the data for any other condition. Furthermore, an obvious temporal frequency tuning was not apparent when the 0.125 c/d condition was used. (In other words, all responses to this spatial frequency appeared to be independent of temporal frequency.) This raised some concern that with low spatial frequencies (the large checks) luminance as well as contrast specific responses were being obtained. To examine this possibility, data was collected in a separate research project at Ferris State College by Anne Johnson-Walker in which four subjects

viewed the stimulus pattern either with or without convex lenses between +1 and +12 D. The same series of spatial frequencies, but only one temporal frequency, were used. The results revealed that for all but the lowest spatial frequency (the large checks), optical blur substantially reduced the amplitude of the PRRP. For the lowest spatial frequency (0.125 c/d) no consistent amplitude reduction was noted as optical blur increased. (Figure 8) This result supports the contention that the measurement of PRRPs in response to very low spatial frequency visual patterns is confounded by retinal potentials which are not contrast specific. Therefore, the 0.125 c/d condition was eliminated from the experimental paradigm.

The amplitude of the averaged PRRP was highly dependent upon both the spatial and temporal frequency characteristics of the stimulus. This was statistically confirmed using a two-way analysis of variance which showed statistically significant F-values for the influence of spatial and temporal frequency on response amplitude. (Table III)

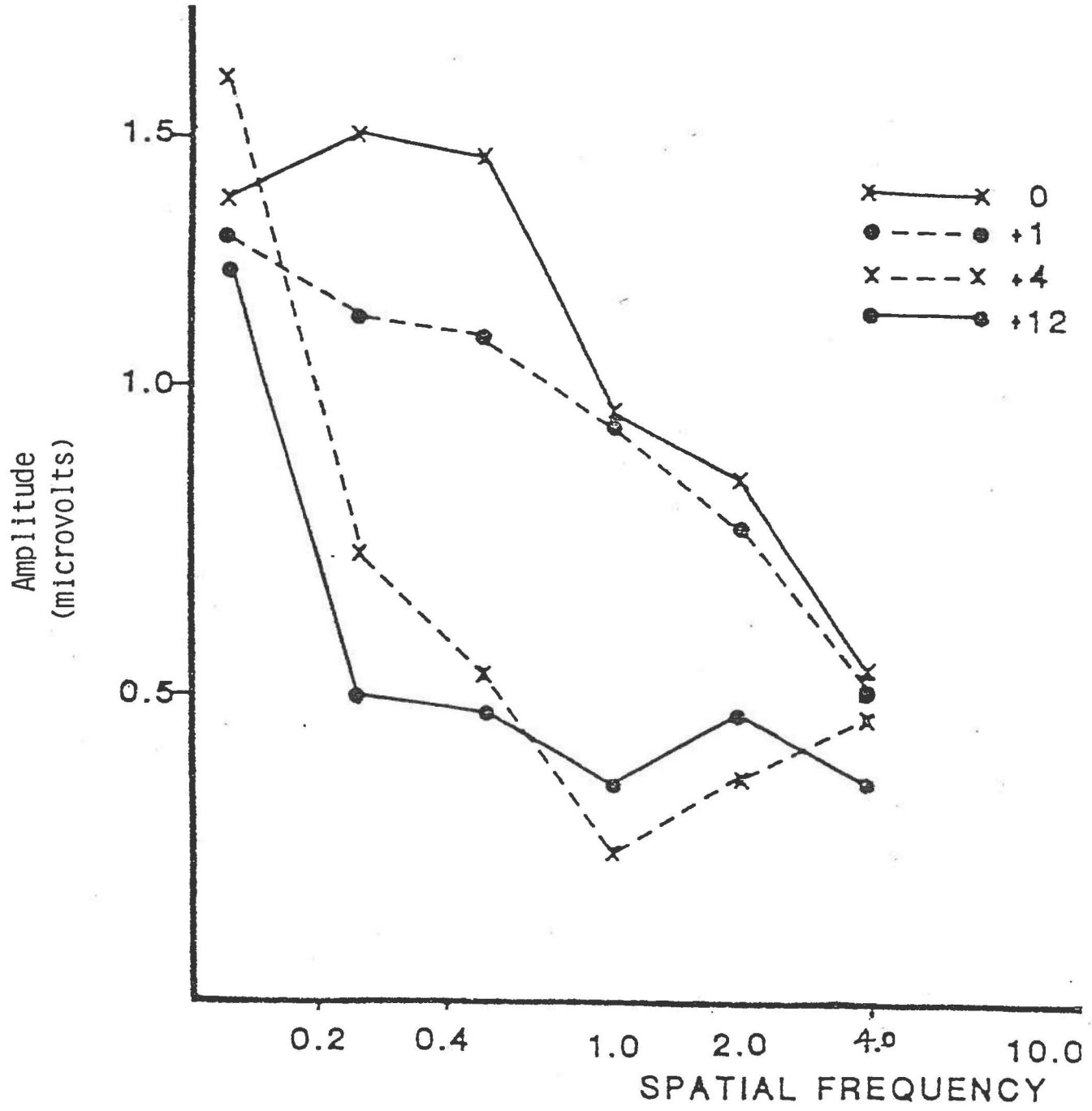

Figure 8

Mean PRRP amplitude as a function of spatial frequency (four subjects). The values in the legend at the upper right in the figure specify the power of the plus lenses worn by the subjects.

Summary of the Two-Way
Analysis of Variance

Source of Variation	Sum of Squares	Degrees of Freedom	Variance Estimate	F Obtained	F Obtained
Spatial Frequency	28.00	4	7.00	52.63	2.39
Temporal Frequency	2.73	4	0.69	2.56	2.39
Spatial-Temporal Frequency-Interaction	2.40	16	0.15	0.56	1.67
Within-Cells	86.56	325	0.27		
Total	119.69	349			

*α = .05

Table III

The amplitude of the averaged PRRP was inversely proportional to the log of the spatial frequency of the stimulus. This relationship held regardless of the temporal frequency of the stimulus. (Figure 9)

This relationship was maintained regardless of the temporal frequency of the stimulus, although the slope of the best fit regression line varied with temporal frequency. The variation of PRRP amplitude as a function of temporal frequency was somewhat less obvious, but for all spatial frequencies tested, some temporal frequency tuning was apparent. The 3.75 Hz temporal frequency produced the largest response amplitudes for high spatial frequencies (1-4 c/d); while the 7.5 Hz temporal frequency yielded the best responses for the low spatial frequencies. (0.25 - 0.50 c/d) (Figure 10)

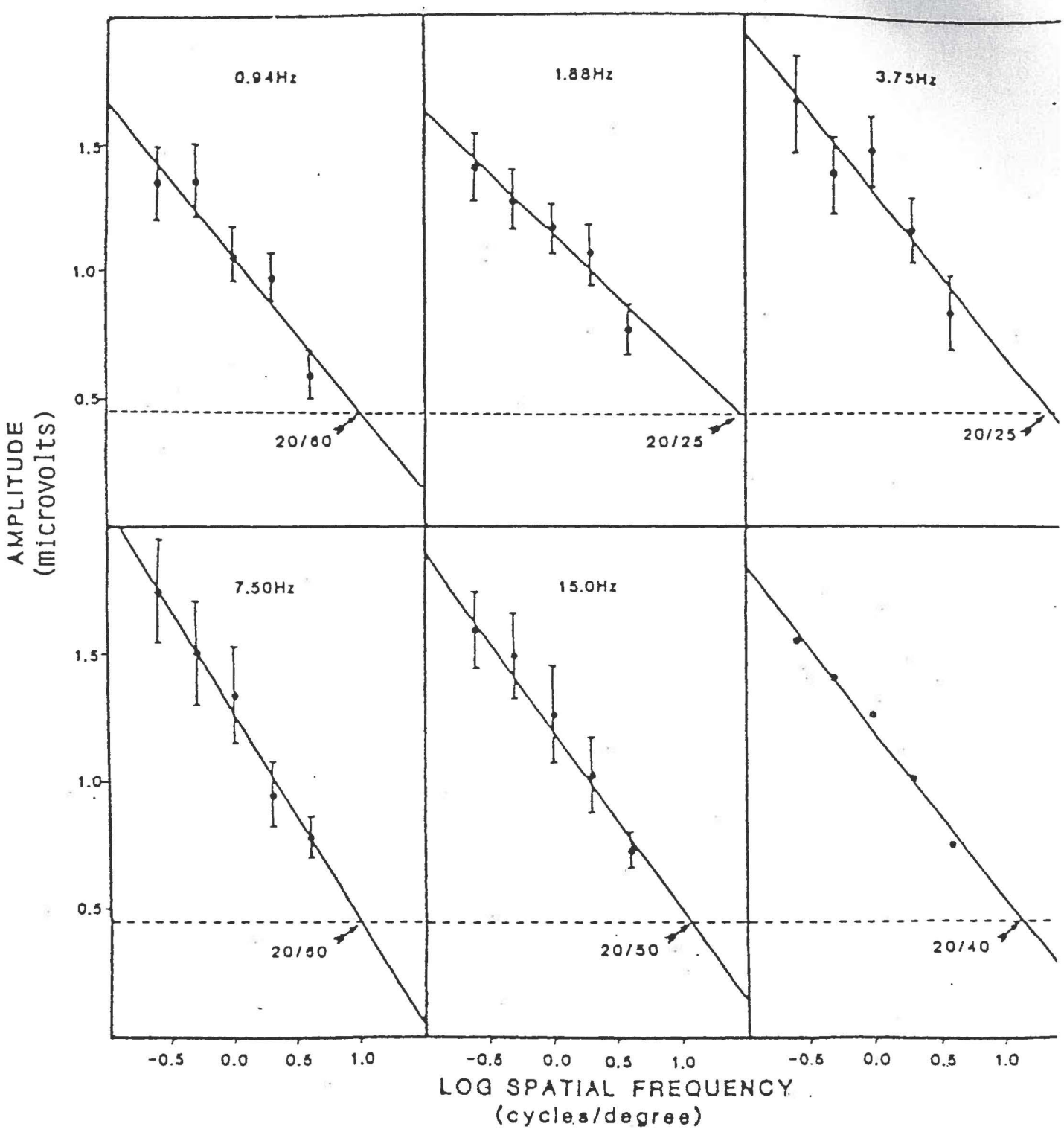

Figure 9

Mean PRRP amplitude as a function of log spatial frequency (14 subjects). Each panel represents mean results for a particular temporal frequency except for the panel on the lower right which represents a grand mean averaged across all temporal frequencies.

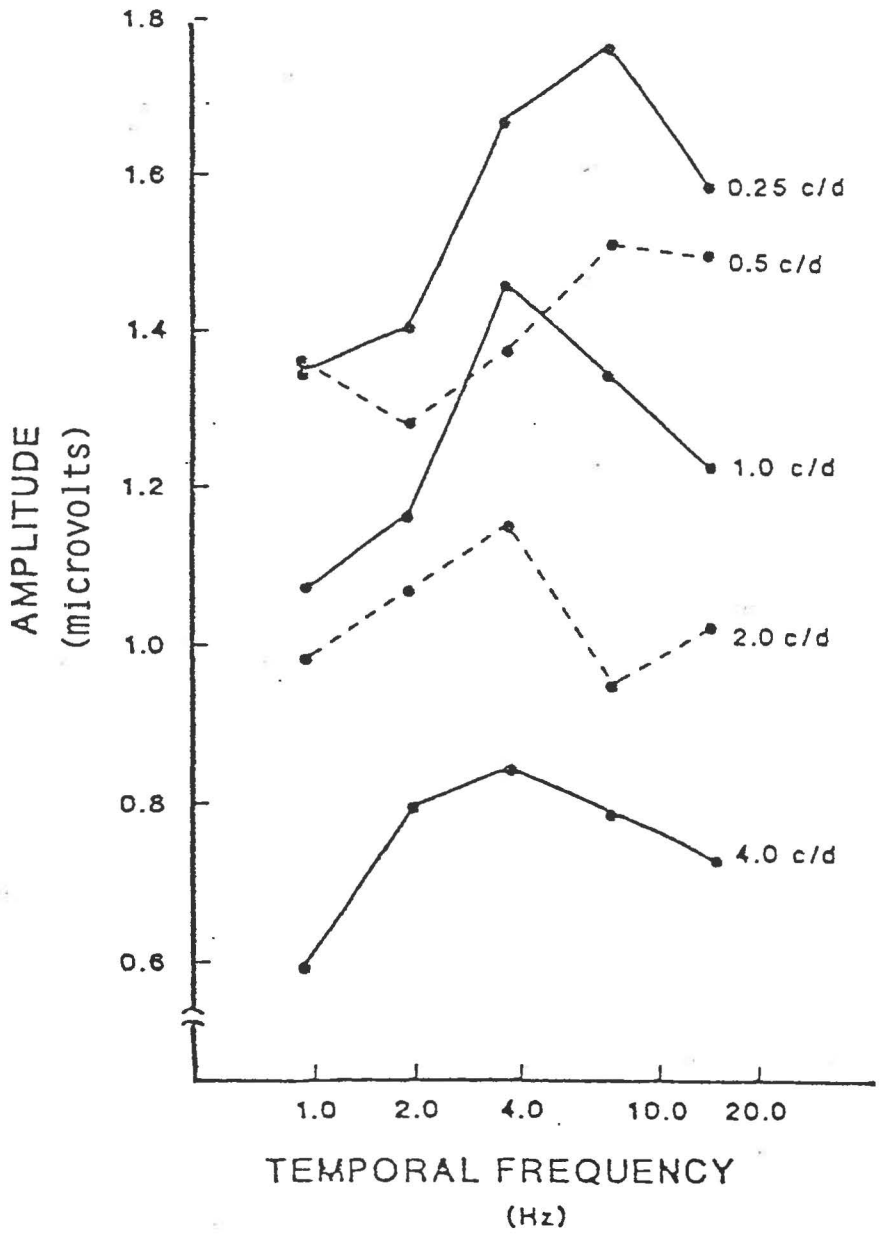

Figure 10

Mean PRRP amplitude as a function of temporal frequency. Each function represents a particular spatical frequency as specified on the right of the figure.

It is unclear at present whether this reflects a spatial frequency dependent shift in the maximum of the temporal tuning function or if the true maximum lies somewhere between 3.75 and 7.50 Hz.

Since the PRRP amplitude versus log spatial frequency functions were approximately linear, a linear regression could be satisfactorily fit to the data points for each temporal frequency. The individual regression lines were then extrapolated to noise level (dashed lines in Fig. 9) and the point of intersection was used to predict visual acuity. (Figure 9) Although all functions are well fit by a linear regression, the regressions fit to the 1.88 and 3.75 Hz conditions yielded the most accurate predictions of visual acuity, approximately 20/25. (Figures 11, 12, 13)

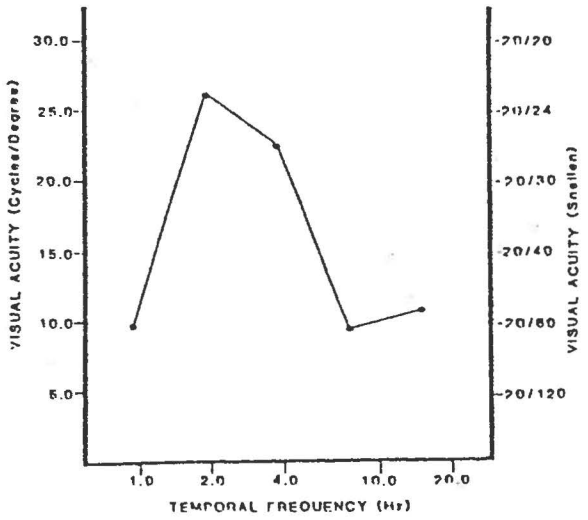

Figure 11

Summary of visual acuity levels obtained when individual regression lines from response amplitude vs. log spatial frequency functions were then extrapolated to noise levels.

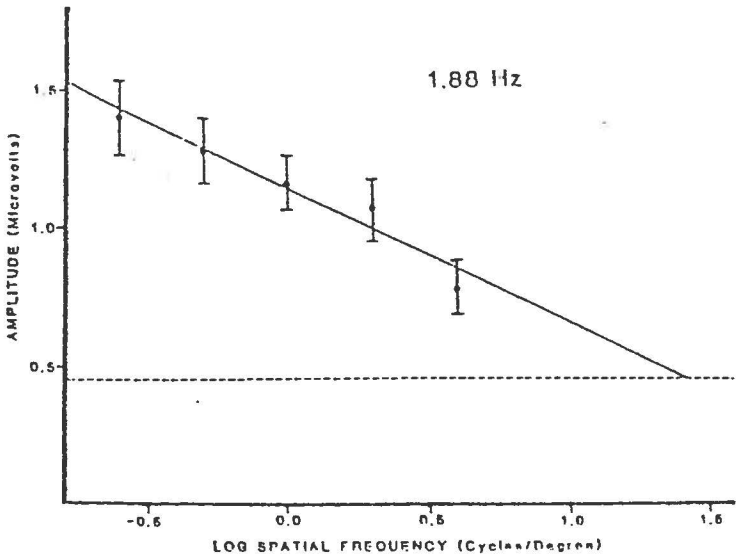

Figure 12

Mean PRRP amplitude as a function of log spatial frequency (14 subjects) for temporal frequency 1.88 Hz.

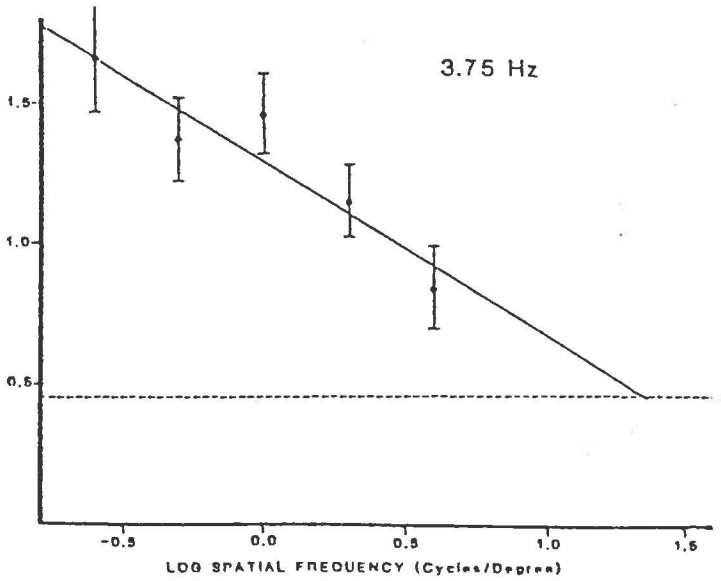

Figure 13

Mean PRRP amplitude as a function of log spatial frequency (14 subjects) for temporal frequency 3.75 Hz.

Discussion

While it is clear that phase-alternating patterns can be used to elicit reliable human PRRPs, the sensitivity of these potentials to variation in stimulus parameters has not been well examined. Researchers have shown that both luminance and wavelength exhibit a significant influence upon the amplitude of the PRRP.[2,3,4] Given the known significance of spatial and temporal parameters for human visual functioning, understanding the influence of these parameters upon the human PRRP becomes particularly important. A more complete understanding of the influence of all stimulus parameters on the PRRP may also clarify some of the issues concerning which retinal components generate these responses. The present results provide a partial description of the spatial and temporal frequency dependence of the PRRP. Clearly, the retinal components generating these potentials are sensitive to both the spatial and the temporal properties of the stimulus.

As previously stated, the amplitude of the PRRP is inversely proportional to the log spatial frequency of the stimulus pattern. Armington et al. reported a similar relationship for two subjects. The decrease in response amplitude at high spatial frequencies (1.0 c/d and higher) is consistent with the human contrast sensitivity function measured both psychophysically[14] and with visual evoked potentials.[15] For low spatial frequencies however, the present results, like the results of Armington fail to

exhibit the decrease in sensitivity found in the human contrast sensitivity function. (Figure 14) This may indicate that the retinal components which contribute to the average PRRP exhibit a low-pass rather than a band-pass spatial frequency tuning characteristic. Given the known band-pass spatial frequency tuning of ganglion cells[16] this seems an unlikely possibility. As an alternative, it is possible that there may be a low frequency roll-off for the spatial frequency tuning function of the contrast specific component of the human PRRP. However, this roll-off may be obscured by the addition of a local luminance response which increases as check size increases.

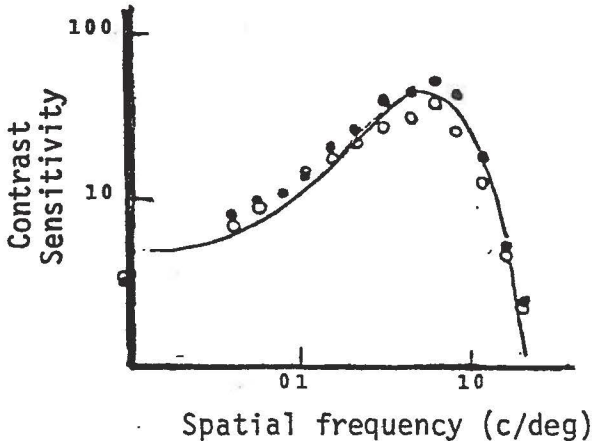

Figure 14

Human contrast sensitivity function.

The temporal frequency dependence of the PRRP also appears to be complex. While there seems to be an optimum temporal frequency for eliciting these retinal potentials, the particular optimum temporal frequency may vary with spatial frequency. Maximum amplitude responses were

consistently obtained with the mid-range of temporal frequencies used (i.e. 3.75 and 7.5 Hz), but the specific temporal frequency producing the largest amplitude varied from 3.75 Hz for high spatial frequencies to 7.5 Hz for low spatial frequencies. An alternative suggestion is that the optimum temporal frequency for generating PRRPs lies somewhere between 3.75 and 7.50 Hz.

The fact that pattern-reversal retinal potentials, when recorded using appropriate temporal frequencies, can yield fairly accurate visual acuity predictions further supports the contention that these responses predominantly reflect macular activity. At the same time the degree of temporal tuning exhibited by these retinal responses is consistent with a proximal retina generation site. It is not clear, however, that the human PRRP can be attributed solely to the ganglion cells (as suggested for cat PRRPs by Fiorentini and Maffei.[11])

In order to further investigate the PRRP etiology, a separate pilot study was undertaken in which three subjects with confirmed glaucoma were given a complete glaucoma work-up which was followed by electrodiagnostic evaluation. This evaluation was similar to testing performed on the 14 normal subjects. We found that the function of the response amplitude found in the glaucoma subjects was noticeably different from that of the normals. (Figure 15)

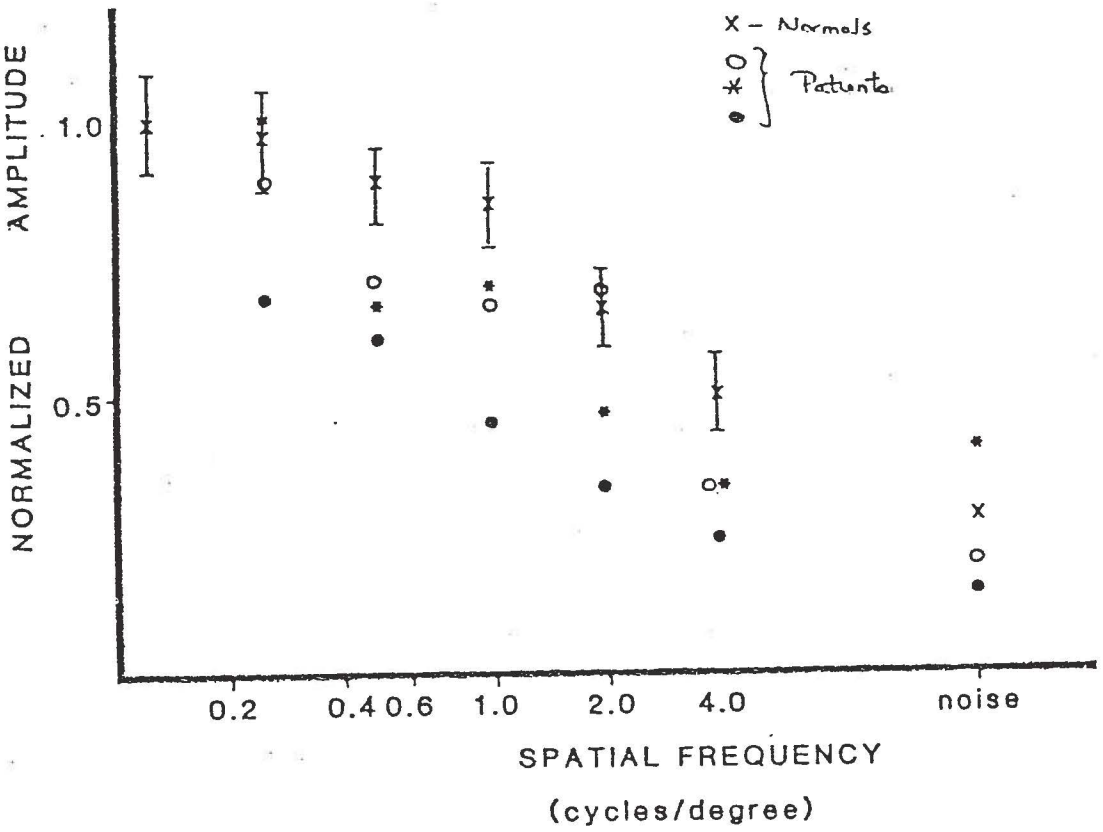

Figure 15

Mean PRRP amplitude as a function of log spatial frequency. (x)'s represent data obtained from 14 normal subjects. Contrast this with data obtained from three patients with confirmed glaucoma.

Figure 15 demonstrates that the glaucoma subjects in this study showed a response function similar in shape to the normals, but significantly reduced in amplitude.

In considering the clinical value of the PRRP, it is important to realize that although these potentials were first described almost twenty years ago, relatively little quantitative study of normal human PRRPs has been completed.

While this investigation provides some quantitative information concerning the variation of these responses with changing stimulus parameters, we still know very little about these retinal responses. Before the use of these potentials can become clinically appropriate, much more must be understood concerning the stimulus specificity of the normal response, as well as its site of generation.

Footnotes

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