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OPTIC ATROPHY REDUCES THE PATTERN-ELECTRORETINOGRAM FOR BOTH FINE AND COARSE STIMULUS PATTERNS

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Summary—1. The pattern electroretinogram (PERG) is thought to be generated by the retinal ganglion cells. For coarse patterns, however, it has been suggested that the PERG is due to a non-linear summation of luminance responses, not generated by the ganglion cells.

2. To test this hypothesis, we recorded the PERG in eight patients with unilateral complete or near complete optic atrophy due to trauma or advanced glaucoma, using the other eye as control. Stimuli were phase-reversing chequerboards with two different check sizes (0.8 and 15°), and full-field flashes.

3. In all cases, the PERG was attenuated (down to 28% of its normal value) with a check size of 0.8°. With a check size of 15°, the PERG was also diminished (to 36%), while the flash responses were not reduced. Any change in the luminance component of the stimulus, for example incomplete balance of light and dark areas, evoked strong responses both in normal eyes and in atrophic eyes.

4. Thus, intact ganglion cells seem to be necessary for a normal PERG, regardless of the coarseness of the pattern. Possibly, different mechanisms (different ganglion cell classes) contribute to the PERG response for different check sizes.

Key words—Pattern ERG; border contrast; luminance; optic atrophy; retinal ganglion cells.

INTRODUCTION

The "pattern-ERG" is a retinal potential evoked by visual pattern stimuli. Ten years ago, Groneberg and Teping (1980) and Maffei and Fiorentini (1981) discovered that atrophy of the retinal ganglion cells leads to a marked reduction in the amplitude of the electroretinogram for pattern stimulation, but not for luminance stimulation. This observation suggested a link between the pattern-evoked electroretinogram (PERG) and the activity of the retinal ganglion cells. However, it is still undetermined how closely the PERG is related to the ganglion cells. If the ganglion cell activity is the source of the PERG, it seems reasonable to expect that the functional properties of the ganglion cells (e.g. Enroth-Cugell and Robson, 1984) should be reflected in the PERG, similar to the cortical VEP. Thus, it is generally assumed (e.g. Maffei, 1982, Discussion p. 9) that optic atrophy, which affects only the retinal ganglion cells and their axons, would not affect the PERG for stimulation with large checks, as large checks present few borders and seem thus ineffective in driving centre-surround type receptive fields. The responses to large-check stimuli are assumed to derive not from the ganglion cells, but from non-linearities of the luminance ERG (Riemslag *et al.*, 1985), which is not (or little) affected by optic atrophy.

This notion has been tested in human beings by only one study: Harrison *et al.* (1987) recorded one patient with optic atrophy due to resection of the optic nerve. This study is often interpreted as having found a strong reduction of PERG using small checks, and an intact PERG using large checks (but see Discussion). As very large check sizes are sometimes used in glaucoma studies (Bach *et al.*, 1988a; Johnson *et al.*, 1989), it is particularly important to know how the response to large checks is related to ganglion cell activity. Thus, we recorded the PERG in patients with unilateral optic atrophy, using the eye with optic atrophy as a model for ganglion cell degeneration and the other eye as a control.

METHODS

We examined eight subjects with unilateral optic atrophy and intact vision in the other eye. Table 1 summarises the clinical data for these patients. With all but one patient (where strabismus was over 20°), stimulation and recording

Table 1. Clinical data are presented for all eight patients

#	Disease	Duration of atrophy (yr)	Acuity normal eye	Acuity atrophic eye	Amplitude normal eye @0.8° (μV)	Amplitude normal eye @15° (μV)	Amplitude atrophic eye @0.8° (μV)	Amplitude atrophic eye @15° (μV)
AS 48	Trauma	56	0.4	Counting f.	1.09	1.39	0.64	0.88
EJ 52	Glaucoma	10	1.2	0.2	5.35	4.25	1.38	0.59
MS 100	Trauma	45	0.6	Amaurosis	2.29	2.73	0.50	1.06
HB 107	Trauma	10	0.4	Amaurosis	1.55	2.15	0.14	0.82
WT 124	Trauma	1	1.2	Defective LP	1.22	1.82	0.85	1.34
HR 132	Trauma	7	1.2	Amaurosis	5.13	5.35	1.19	1.75
RG 140	Trauma	4	1.0	Amaurosis	1.44	1.86	0.15	0.26
KG 144	Glaucoma	56	0.3	Amaurosis	1.38	2.09	0.51	1.17
Mean		23.6			2.43	2.71	0.67	0.98
SD		24.2			1.77	1.38	0.45	0.46

Individual PERG amplitudes for each eye and for the two check sizes, as calculated by Fournier analyses of the record shown in Fig. 1, are tabulated on the right.

were simultaneous in both eyes. Strabismus, if present, was corrected using prisms over one or both eyes. We will often refer to eyes with optic nerve atrophy as "atrophic eyes", without implying any overt morphologic changes of the eyeball.

The stimuli used in the experiments were presented on a visual display unit with a spatial resolution of 480 × 390 pixels; the frame rate was 71 Hz. The following stimuli were applied: a phase-reversing checkerboard with a mean luminance of 50 cd/m^2 and a temporal frequency of 7.8 reversals/s (corresponding to 3.9 Hz) and check sizes of 0.8° and 13 × 17° (we will refer to the 13 × 17° as "15°" throughout this report). In the "full screen" condition, the checkerboard covered the entire screen (26 × 34°). In the "bright surround" condition, the checkerboard was visible within a circle of 15° in dia and was surrounded by a homogeneous field of 120 cd/m^2; check size was thus either 0.8 or ≈ 7°. The borders of the checks met at the centre of the screen for all check sizes. In addition to these pattern stimuli, for luminance flicker stimulation the luminance of the homogeneous screen was switched between 0.3 and 100 cd/m^2 as a square-wave function of time with a bright:dark ratio of 0.1:1.0 (in patients # 48 and # 52, the bright:dark ratio was 1:1). The room was dimly illuminated (47 lx).

A small cross in the centre of the screen served as a fixation point. To enhance their attention, subjects had to report a randomly chosen digit which appeared every 5–10 s for 600 ms at the fixation point.

ERG responses were recorded with DTL electrodes (Dawson *et al.*, 1979; Thompson and Drasdo, 1987) placed near the lower limbus, using an ipsilateral gold cup electrode as reference. The signals were amplified using a bandpass of 1–70 Hz (first-order filters) and recorded by a computer. Analogue to digital conversion was performed with a resolution of 12 bits and a sampling rate of 500 Hz. The computer also generated the stimuli. Averaging was phase-locked to the frame rate (thus avoiding latency jitter) and occurred only on even reversals, i.e. the sweep was triggered only when the top left square became bright. Thus, the luminance on-response was not suppressed by averaging it with the off-response (Spekreijse *et al.*, 1973), and luminance responses caused by imbalance through eccentric fixation could not mimic pattern responses. Sweeps (typically 70 per recording) of 512 ms duration were averaged and continuously displayed. A sweep was rejected whenever the signal exceeded the value of ± 100 μV. The measurements were performed in a blocked design using an interleaved stepwise sweep technique, stepping through all stimuli (checkerboards of 0.8 and 15° check size and flicker) 14 times, leading to a total of 140 sweeps for each condition.

To facilitate Fourier analysis of the steady-state responses, the reversal frequency was adjusted to yield an integer number of reversals per sweep, thus eliminating "spill over" effects. Evoked potential amplitude was measured in the frequency domain as the magnitude at the stimulation rate.

RESULTS

Figure 1 presents the recordings from all subjects for stimulus conditions of 0.8° (top) and 15° checks (centre) and flicker (bottom). The traces are arranged such that the normal eye is on the left, and the atrophic eye on the right. For pattern stimulation of 7.8 reversals/s (3.9 Hz), four peaks are evident in the recording

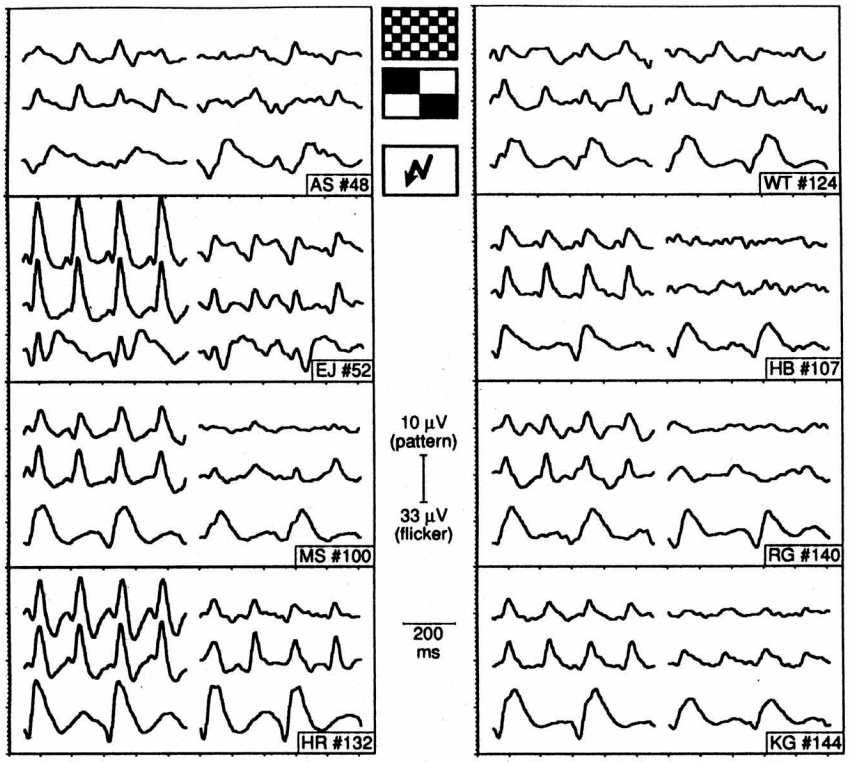

Fig. 1. The recordings from all subjects using 0.8° (top) and 15° checkerboards, and flicker (bottom of each triplet). The traces are arranged such that responses from the normal eye are shown on the left, and those from the atrophic eye to the right. Calibration is identical for all pattern tracings, the flicker tracings are scaled down to one-third. In all subjects the PERG amplitude was lower, by varying degrees, in the atrophic eye compared to the fellow eye.

interval of 512 ms; in the case of flicker stimulation with 3.9 Hz two peaks appear. In all subjects the PERG amplitude was lower in the atrophic eye than in the fellow eye for both 0.8 and 15° checks, although to varying degrees. The flicker response, while always present, differed between the eyes in shape.

Table 1 presents quantitative PERG amplitudes as calculated by Fourier analysis. In Fig. 2(a), the mean amplitudes can be compared between eyes and check sizes. The PERG amplitude is similar to 0.8 and 15° checks in normal eyes. In the atrophic eyes, the amplitude is reduced for both check sizes (28% of the normal response for 0.8°, and 36% for 15°). The difference of the mean amplitude between the normal and the atrophic eyes was statistically significant (Wilcoxon test for matched pairs, $P = 0.012$ for both check sizes). To assess amplitude variability, the data are re-plotted in Fig. 2(b) after normalisation to the amplitude in the normal eye at 15° for each subject. The relative variability within subjects is thus shown to be low for the normal eyes (coefficient of variance = 23%), indicating little within-session variability (possibly due to the interleaved step-wise sweep), but high between normal and atrophic eyes (coefficient of variance = 52%), indicating a wide range of pathologic changes.

Figure 3 displays the recordings from all subjects, where the "bright surround" condition with a check size of 0.8° (top) and 7° (bottom) was included in the recording protocol. Again, response from the normal eye are shown to the left, those from the atrophic eye to the right. Compared to Fig. 1, the overall amplitudes are lower due to the smaller stimulus area. In the recording condition with the bright surround, the relative response to large checks is even lower in the atrophic eye than in the stimulus condition without the bright surround.

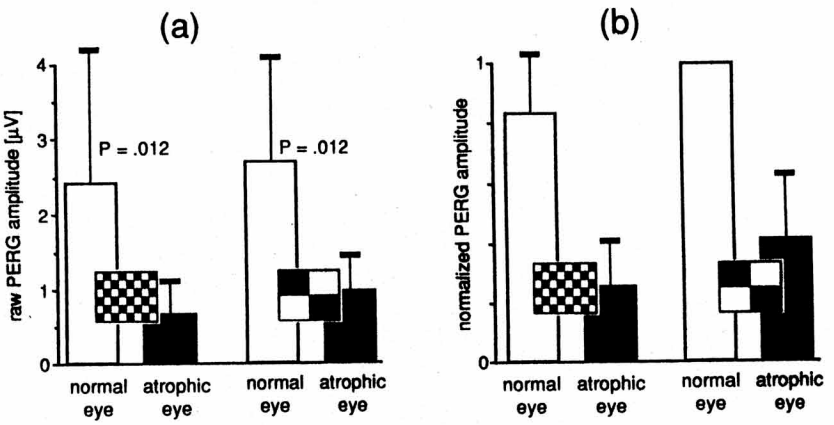

Fig. 2. Grand mean of raw PERG amplitudes (+SEM) across all eight subjects. Amplitudes were calculated by Fournier analysis from the recordings in Fig. 1. The PERG amplitude is similar to 0.8 and 15° checks in normal eye. In the atrophic eyes, the amplitude is lower for both check sizes (down to 28% for 0.8° and to 36% for 15°). (b) As in (a), but normalised to the amplitude in the normal eye @15° for each subject.

An interesting phenomenon occurred with asymmetric stimulation, i.e. incomplete balance between the bright and dark parts of the stimulus: Fig. 4 (top) shows the PERG using a pure pattern stimulus with four large squares covering the entire screen. When one square was covered with a piece of cardboard with intermediate luminance (Fig. 4, lower panel), introducing an unbalanced luminance component into the stimulus, a strong response to every second stimulus resulted. The "pattern" responses are superimposed on to the flanks of the luminance response. With the symmetric pattern stimulus (top), the large luminance re-

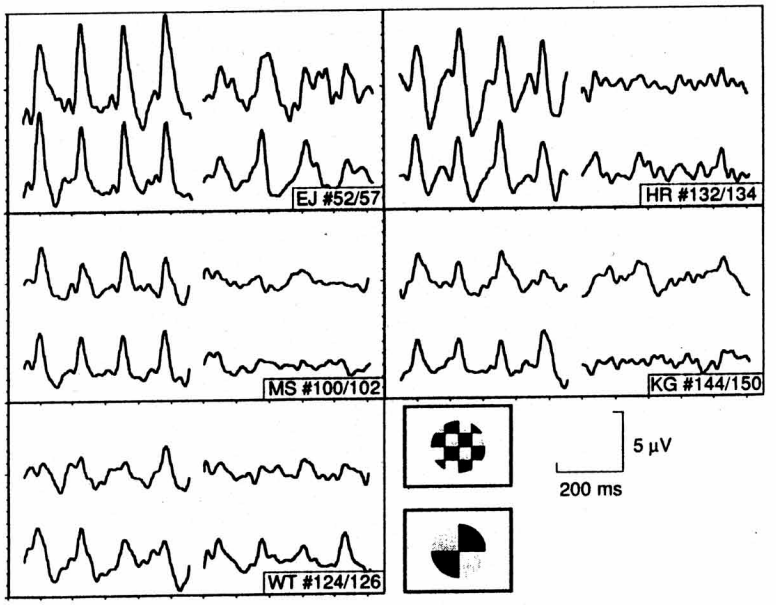

Fig. 3. PERG tracings from all subjects in the "bright surround" condition for 0.8° (top) and 7° (bottom) check size. In this recording condition, the response to large checks in the atrophic eye is even lower than in the stimulus condition without the bright surround.

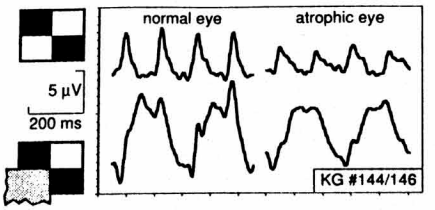

Fig. 4. Top: PERG in patient 144, normal eye left, atrophic eye right, using a 15° checkerboard stimulus. Bottom: as above, except that one-quarter of the screen was covered with a piece of cardboard, introducing an unmatched luminance component into the stimulus. While the pattern-responses of the atrophic eye are half those of the normal eye (top), luminance-responses of one-half the temporal frequency and nearly equal size are evoked in both eyes, with the larger "pattern"-responses superimposed on to the luminance-response in the normal eye.

sponses nearly cancelled each other. This result could only be obtained by triggering the averager correctly (see Methods), as indiscriminate triggering averages the on- and off-components, concatenated with the next off–on-response. The on- and off-components mutally cancel in the averaged record and lead to a response which is indistinguishable from a normal PERG (Spekreijse *et al.*, 1973). This finding prompted us to control carefully the fixation in the observers with optic atrophy, as eccentric fixation off the horizontal or vertical meridian would lead to asymmetric stimulation, evoking luminance responses. This is mandatory when large checks are used.

DISCUSSION

The present results indicate the following: (1) PERG amplitudes of the normal eyes showed a large interindividual variability; (2) PERG amplitudes to 0.8 and 15° check size were similar; (3) PERG amplitudes were lower in all atrophic eyes than in the normal eyes; (4) PERG amplitudes in most atrophic eyes were still clearly above noise level at both 0.8 and 15° check size; (5) reduction of PERG amplitude was nearly as strong at a check size of 15° as at a size of 0.8°.

Finding (1), high variability, is well known for the PERG (Holopigean *et al.*, 1988), but does not affect the conclusions from the present study: first, the *ratio* in individual eyes between the response to 0.8 and 15 checks had a lower variability between eyes [Fig. 2(b)]. Secondly, the intraindividual variability of PERG amplitude is lower than the interindividual variability, which is utilized in the present study by comparing the normal to the atrophic fellow eye.

Finding (2), lack of spatial tuning, underscores that attenuation of low spatial frequencies critically depends on stimulus paramaters. Conditions favouring spatial selectivity include low luminance, fast sinusoidal modulation in time and space, low contrast and pattern onset stimulation (Korth, 1983; Hess and Baker, 1984; Korth and Rix, 1985; Bach and Speidel-Fiaux, 1989); conditions favouring a flat tuning curve, as used here, include high luminance, square-wave modulation in time and space, high contrast and pattern reversal stimulation (Korth, 1981; Arden *et al.*, 1982; Trick and Wintermeyer, 1982; Vaegen *et al.*, 1982; Sokol *et al.*, 1983). The observation that patterns with few contrast borders (15° checks: 4 borders) and patterns with many contrast borders (0.8° checks: ≈ 700 borders) evoke a PERG of roughly equal amplitude, does not rule out retinal ganglion cells as generators of the PERG: retinal ganglion cells respond well to luminance flicker (e.g. Zrenner, 1983), and for a single retinal locus, a high-contrast, phase-reversing checkerboard is comparable to a flicker stimulus with a bright: dark ratio of 1:1.

Finding (3), reduction of the 0.8°-amplitude in optic atrophy, is the expected classical finding (see Introduction).

Findings (4) and (5) however, are both not expected by the current interpretation of the PERG (e.g. Maffei and Fiorentini, 1990). Could these results have been brought about by experimental artifacts? Finding (4), the surprisingly high residual response in some of the atrophic eyes, could be due to cross-talk from the good eye. Although we used a derivation (ipsilateral outer canthus reference, Berninger, 1986) that showed no obvious cross-talk under the given signal-to-noise ratio, this possibility cannot be entirely ruled out. Alternatively, it could represent residual ganglion cell activity in spite of seemingly total atrophy as reported by Kratz (1990). He sectioned the optic nerve in cats and found after 7 months' survival time that the PERG amplitude was still 20% of its normal value and, histologically, 11% of the retinal ganglion cells remained.

Could finding (5), the strong reduction of the 15° response, be due to artifacts? We think not: cross-talk from the good eye would enhance, rather than diminish the response. Similarly stray light stimulation of the periphery would increase, rather than decrease the response. In the "bright surround" condition, peripheral stray light stimulation is suppressed. Under this

condition, the relative reduction of PERG amplitude at 15° vs 0.8° checks was even more pronounced (cf. Figs 1 and 3).

Is the PERG perhaps generated in different eccentricity ranges for large and small check sizes? Pfeiffer *et al.* (1990) compared PERG responses for central stimulation ($\epsilon < 6°$) and peripheral stimulation ($\epsilon \geq 6°$) using both 0.8 and 7° checkerboards. They found that the ratios of the responses evoked by 0.8 and 7° checks were equal under the two eccentricity ranges. We conclude, that the small- and large-check responses were generated at similar retinal sites with respect to eccentricity.

Finding (5), reduction of the 15° response in optic atrophy, is not entirely without precedents: Harrison *et al.* (1987) examined a patient with optic atrophy due to surgical resection of the optic nerve. They found reduced responses using small to medium check-size patterns (below ≈ 3°), while the responses to 6.7° checks were found to be normal (their Fig. 5). However, at all other check sizes tested (excepting 6.7°, but including 13,5°), PERG amplitudes were strongly reduced in the atrophic eye (Fig. 7 in Harrison *et al.*, 1987). In this light, there is no contradiction to the present findings. A previous study from our laboratory of five different patients with optic atrophy (Bach *et al.*, 1988b) also found strong reduction of the large check response in optic atrophy.

It is currently unclear whether only the ganglion cells are affected in optic atrophy: Van Buren (1963) observed a "cystic degeneration in the inner nuclear layer" after a lesion of the chiasm. More recent reports by Holländer *et al.* (1984) and Wässle *et al.* (1987) suggest that atrophy of the retinal ganglion cells does affect amacrine or bipolar cells transsynaptically. Odom *et al.* (1990) recently reported a 40% reduction of the second harmonic component of the flicker ERG in glaucoma. This could either reflect a change in distal retina, or indicated that the non-linearities in the flicker ERG reflect ganglion cell activity.

There is increasing acceptance of the hypothesis that the PERG is dominated by different mechanisms for high and low spatial frequencies (Drasdo *et al.*, 1987, 1990; Bach *et al.*, 1988a; van den Berg and Boltjes, 1988). The present findings show that both mechanisms are affected by optic atrophy. This suggests that both the large and small check responses are generated by the ganglion cells, though possibly by different types of ganglion cells.

If the responses to 15° checks indeed reflected the function of the retinal ganglion cells, the clinical usefulness of the PERG could be enlarged. Poor image formation on the retina (due to media opacities or inappropriate accommodation) strongly attenuates the PERG to stimulation with small checks. Such retinal image degradation could be largely avoided by using patterns with large checks.

In conclusion, the present results indicate that for slowly pattern-reversing, high-contrast checkerboard stimuli the PERG reflects retinal gangion cell function, regardless of the check size. This applies even to very large checks, where the response may be related to the flicker response of phasic ganglion cells.

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