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Impaired VEP after photostress response in multiple sclerosis patients previously affected by optic neuritis

Vincenzo Parisi[a,b,*], Francesco Pierelli[c], Rita Restuccia[c], Maria Spadaro[c], Leoluca Parisi[c], Gaspare Colacino[a], Massimo G. Bucci[a,b]

[a]*Cattedra di Clinica Oculistica, Università di Roma 'Tor Vergata' c/o Complesso Integrato Columbus, Via della Pineta Sacchetti 506, 00168 Rome, Italy*
[b]*Fondazione per l'Oftalmologia G.B.Bietti, Piazza Sassari 5, 00162 Rome, Italy*
[c]*Istituto di Clinica delle Malattie Nervose e Mentali, Università di Roma 'La Sapienza', Viale dell'Università 30, 00161 Rome, Italy*

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Abstract

The aim of our work was to evaluate if an optic nerve involvement (multiple sclerosis patients previously affected by optic neuritis) may induce any change in visual evoked potential (VEP) after photostress response. VEP in basal conditions and after photostress were assessed in 10 patients with defined multiple sclerosis without a history of optic neuritis (MSWO); in 14 patients with defined multiple sclerosis previously affected by optic neuritis but with complete recovery of the visual acuity (MSON) and in 14 age-matched controls. In order to complete the investigation of the retinal function, Transient Pattern electroretinogram (PERG) and steady-state focal-ERG (counterphased gratings presented at 8 Hz in the macular region) were performed in MSON patients only. In MSWO eyes VEP parameters in basal condition and after photostress did not undergo significant changes compared to controls (ANOVA; $P > 0.05$). In MSON eyes we observed basal VEP with delayed P100 peak latency and reduced N75-P100 amplitude when compared with the control ones ($P < 0.01$). In MSON eyes the parameters of VEP after photostress underwent larger changes and longer recovery time (RT) than in control and MSWO eyes ($P < 0.01$). In addition; in MSON eyes we found increased transient PERG P50 latency ($P < 0.01$) and reduced P50-N95 amplitude ($P < 0.01$); Focal-ERG (that displays a major component at 16 Hz; 2nd harmonic:2P) with reduced 2P amplitudes and delayed 2P phases ($P < 0.01$). Our results indicate that patients previously affected by optic neuritis present an abnormal VEP after photostress response and this may be ascribed predominantly to an involvement of the inner retinal layers as indicated by the concomitant impairment of PERG and focal-ERG responses. © 1998 Elsevier Science Ireland Ltd.

Keywords: Visual evoked potentials; Photostress; Pattern-electroretinogram; Focal-electroretinogram; Optic neuritis; Multiple sclerosis

1. Introduction

The recording of visual evoked potentials (VEPs) after dazzling of the central retina (photostress) has been proposed as an index of the macular function (Franchi et al., 1987). Photostress induces transient VEP changes consisting in an increase in latency and a decrease in amplitude. Serial recordings allow us to observe, in normal subjects, a complete recovery of VEP waveform (recovery time after photostress, RT) in a range of between 68 and 78 s after dazzling (Parisi and Bucci, 1992). A delay of RT has been observed in subjects with maculopathy when compared to controls, and this has been correlated to the extent of the anatomo-functional changes in the photoreceptor-pigmented epithelium system (Franchi et al., 1987). Furthermore, the functional integrity of the inner retinal layers of the central retina, seems to play a role in the functional recovery of the VEP after photostress. This derives from the longer RT observed in patients with ocular hypertension and glaucoma (Bucci et al., 1991; Parisi and Bucci, 1992); and in diabetics with or without retinopathy (Parisi et al., 1994, 1995, 1997; Uccioli et al., 1995).

The aim of our work was to evaluate if a previous optic nerve involvement (optic neuritis in multiple sclerosis patients) may induce an impaired VEP after photostress response.

* Corresponding author. Cattedra di Clinica Oculistica Università di Roma 'Tor Vergata', Via Santa Maria Goretti 66, 00199 Rome, Italy. Tel.: +39 6 86216880; e-mail: vparisi@mbox.vol.it

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2. Methods and materials

Twenty-four patients (9 males and 15 females; mean age 32.4 ± 7.1 years) with a diagnosis of definite multiple sclerosis according to the criteria previously proposed (Poser et al., 1983) were examined.

An ophthalmological examination including anterior segment biomicroscopy, visual acuity, applanation tonometry and ophthalmoscopy, was performed in all subjects tested. Inclusion criteria for the study were: refractive errors, when present, contained within −2 and +2 spherical dioptries; no concomitant ocular or systemic disease.

Ten patients (MSWO group) were never affected in either eye by optic neuritis; 14 patients (MSON group) were previously affected by optic neuritis with a complete recovery of the visual acuity (10/10). According to the above mentioned criteria we considered as reliable data those obtained in 10 eyes from the MSWO group and 19 eyes from the MSON group. They were compared to 14 eyes from 14 control age-matched subjects.

In control and multiple sclerosis patients we assessed VEP in basal condition and after photostress. In addition; in order to complete the investigation of the retinal function pattern electroretinogram (PERG) and focal-ERG (FERG) were performed in those patients in whom we found a longer RT with respect to our normal limits (mean values of control + 3 SD; see below).

The subjects under examination were seated in a semi-dark room, acoustically isolated, in front of the display that was surrounded by a uniform field of luminance of 5 cd/m^2. Prior to the experiment, each subject was adapted to the ambient room light for 10 min and the pupil diameter was about 5 mm. Mydriatic or miotic drugs were never used. The stimulation was monocular, after occlusion of the other eye.

Informed consent was obtained from each subject enrolled in the study.

2.1. VEP in basal condition and after photostress

VEP was recorded using the method previously described (Bucci et al., 1991; Parisi and Bucci, 1992; Parisi et al., 1994, 1995, 1997). The visual stimuli were checkerboard pattern (contrast 70%; mean luminance 100 cd/m^2) generated on a TV monitor and reversed in contrast at the rate of two reversals/s. At the viewing distance of 114 cm the single check edge subtended 15 min of visual arc. The screen of the monitor subtended 18° and in order to maintain stable fixation; a red small target (0.5°) was placed in the center of stimulation field.

Cup shaped electrodes of silver-silver-chloride were fixed with collodion in the following positions: active electrode in Oz; reference electrode in Fpz; ground in left arm. The interelectrode resistance was kept below 3 kW. The bioelectric signal was amplified (gain 20 000), filtered (band-pass 1–100 Hz) and averaged with automatic rejection of artifacts by BM 6000 system (Biomedica Mangoni, Pisa, Italy).

The recording session began with a preliminary experiment in which at least two VEP were recorded averaging over 100 stimulus periods; excluding the time of artifacts. The analysis time was 500 ms.

The resulting waveforms were stored and superimposed to check for the repeatability of the results. The transient response was characterized by several waves with 3 peaks of negative-positive-negative polarity, respectively. In normal subjects these peaks have the following latencies: 75; 100 and 145 ms. After this preliminary trial; a control VEP was recorded, reducing the average to 40 events per trial (with no more than two sweeps discarded because of artifacts). This VEP record was defined as 'basal' and it was kept on display on the computer screen. Six consecutive records were taken for successive periods of 20 s each (40 averaging every 20 s of recording and the corresponding record displayed on the screen) in order to check the repeatability of the waveform obtained.

Photostress was induced for 30 s by means of a circular diffusing surface (the bulb of a 200 W lamp) that was centrally fixated by the subject from a distance of 20 cm and produced a central scotoma of 6° of diameter. During the photostress procedure each of the subjects looked directly into the center of the light, and the pupil diameter was about 2 mm.

Immediately after the end of photostress, fixation was shifted to the pattern stimulus and recording of VEPs started. The small red target was perceived by all subjects notwithstanding the presence of scotoma. Several records were taken for successive periods of 20 s each and stored on the computer screen.

The recordings were performed until the VEP waveform was superimposable on the basal record and the corresponding time was considered as 'recovery time after photostress' (RT).

In each subject tested the signal-to-noise ratio (SNR) was assessed twice. The noise was measured while the monitor was screened using cardboard. In the first SNR; the noise was evaluated averaging 40 events, as the number of sweeps averaged in the trials recorded 'after photostress'; in the second SNR, the noise was evaluated as events as the number of sweeps counted in the final averaging process. We accepted 'VEP after photostress' responses in which both SNR were >2 and the subject tested was included in the study.

2.2. Pattern electroretinogram

The visual stimuli were checkerboard patterns (contrast 70%, mean luminance 100 cd/m^2) generated on a TV monitor and reversed in contrast at the rate of two reversal/s. At the viewing distance of 114 cm the single check edge subtended 15 min of visual arc, because this smaller size is considered 'optimal to stimulate the fovea' also in pattern

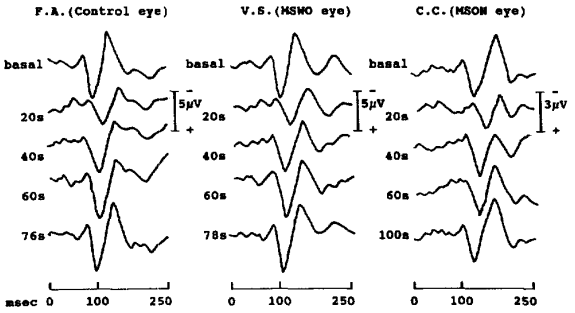

Fig. 1. VEP layout of subjects F.A. (control eye), V.S. (MSWO eye) and C.C. (MSON eye) in basal condition and 20, 40 and 60 s after photostress. In comparison with the control and MSWO eye records, in the MSON eye, VEP recorded at 20, 40 and 60 s after photostress show a longer P100 latency and a reduced amplitude. The VEP are superimposable on the basal waveform (recovery time) at 76 s in the control eye, at 78 s in MSWO eye and at 100 s in the MSON eye.

electroretinography (Tomoda et al., 1990; Celesia et al., 1993). The screen of the monitor subtended 18° and in order to maintain stable fixation, a red small target (0.5°) was placed in the center of the stimulation field.

The bioelectrical signal was recorded by means of platinum hook electrodes inserted into the external corner of the inferior eyelid. Electroretinograms were derived bipolarly between the tested (active electrode) and the patched (reference electrode) eye using a method previously described (Fiorentini et al., 1981). Local anesthesia was provided by application of Novesine 0.4%.

The ground electrode was in Fpz. The interelectrode resistance was lower than 3 kW. The signal was amplified (gain 50 000), filtered (band-pass 1–30 Hz) and averaged with automatic rejection of artifacts (200 events were averaged for every trial).

The analysis time was 250 ms. We assessed records of transient PERG at least twice in order to check the repeatability of the waveform obtained. The transient PERG response is characterized by 3 subsequent peaks of negative-positive-negative polarity, respectively. In normal subjects and in conditions of our experiment; these peaks have the following mean latencies: 35; 50 and 95 ms.

2.3. FERG

FERG was recorded using a method previously described (Falsini et al., 1992). Pattern stimuli were sinusoidal gratings of 2 c/degree spatial frequency, 90% contrast, stimulating the central 9 × 9 degrees of visual field, generated in the TV monitor (110 cd/m^2 mean luminance) and modulated in counterphase at 8 Hz. In order to minimize the stray light effects (Brindley and Westheimer, 1965) an equilluminant large surround (150 × 150 cm) was peripherally provided.

In order to maintain stable fixation, a red small target (0.5°) was placed in the center of the stimulation field. The bioelectrical signal was recorded using the same method employed in PERG recordings (position of electrodes, gain, band-pass) and 600 events free from artifacts were averaged for every trial. The analysis time was 125 ms.

The FERG in response to 8 Hz modulated light or counterphased gratings display a major component at 16 Hz (2nd harmonic:2F for light stimulation and 2P for pattern stimulation) (Baker and Hess, 1984; Baker et al., 1988; Porciatti, 1987; Porciatti et al., 1989). Discrete Fourier analysis was performed off-line by BM 6000 in order to isolate PERG 2nd harmonic (2P); and the peak-to-peak amplitude (μV) and phase (degrees) were measured.

We assessed records of FERG at least twice in order to check the repeatability of the waveforms obtained.

We accepted PERG and FERG signals with signal-to-noise ratio >2. The noise was measured by recording the bioelectrical signals (200 events were averaged) while the monitor was screened by a cardboard and a noise <0.1 μV (mean 0.085 μV) was observed in all subjects tested.

For all electrophysiological examinations the peak latency and the peak amplitude of each of the averaged waves were measured directly on the displayed records by means of a pair of cursors.

The differences between control; MSON and MSWO eyes were statistically evaluated with one-way analysis of variance for repeated measures (ANOVA).

3. Results

The main clinical and electrophysiological data of the MSON patients are reported in Table 1.

3.1. Basal VEP

Examples of records of one control eye, one MSON eye and one MSWO eye are shown in Fig. 1 (see basal). The mean data of P100 latency and N75-P100 amplitude are presented in Table 2 (see basal).

In MSWO eyes P100 latency and N75-P100 amplitude were similar to those of controls (P100 latency: $F(1,23) = 4.38$, $P = 0.048$, N75-P100 amplitude: $F(1,23) = 2.80$, $P = 0.109$). In MSON eyes P100 latency was significantly delayed ($F(1,32) = 58.99$, $P < 0.01$) and N75-P100 amplitude was significantly reduced ($F(1,32) = 12.52$, $P < 0.01$) when compared with the control ones.

3.2. VEP after photostress

Examples of records of one control eye, MSON eye and MSWO eye are shown in Fig. 1. The mean data are presented in Figs. 2 and 3 and in Table 2.

In control eyes at 20 s after photostress; an increase in P100 latency and a decrease in N75-P100 amplitude were observed. At 40 s and 60 s after photostress the P100 latencies were shorter with respect to the values observed at 20 s, but they were still longer than in the basal VEP; the amplitudes increased with respect to the values observed at 20 s,

Table 1
Clinical and electrophysiological data in MSON patients

Patient	Sex	Age (years)	Time elapsed from last ON episode (months)	PERG P50 latency (ms)	PERG P50-N95 amplitude (μV)	Focal-ERG 2P amplitude (μV)	Basal VEP P100 latency (ms)	Recovery time (s)
A.P.	M	26	R 18	R 64	R 0.8	R 0.6	R 116	R 90
			L 23	L 70	L 0.8	L 0.4	L 128	L 90
A.S.	F	28	R 19	R 60	R 0.4	R 0.3	R 124	R 93
			L 20	L 64	L 0.5	L 0.2	L 124	L 86
P.N.	F	40	R 21	R 63	R 0.4	R 0.3	R 115	R 95
			L 18	L 70	L 0.5	L 0.2	L 136	L 98
C.R.	F	38	R 22	R 66	R 0.3	R 0.2	R 110	R 98
			L 22	L 76	L 0.5	L 0.3	L 129	L 90
A.R.	F	38	R 24	R 73	R 0.5	R 0.3	R 128	R 90
			L 24	L 67	L 0.6	L 0.4	L 132	L 90
R.C.	M	40	L 18	L 70	L 0.7	L 0.6	L 118	L 90
F.M.	F	29	R 20	R 64	R 0.6	R 0.5	R 118	R 103
S.C.	F	30	R 14	R 70	R 0.6	R 0.6	R 122	R 95
C.C.	F	26	R 18	R 62	R 0.7	R 0.8	R 108	R 100
C.V.	F	22	L 14	L 63	L 0.8	L 0.5	L 108	L 95
C.S.	F	20	R 18	R 69	R 0.7	R 0.6	R 112	R 90
D.A.	F	22	L 14	L 73	L 0.6	L 0.8	L 118	L 103
C.M.	F	40	R 24	R 74	R 0.4	R 0.3	R 138	R 98
B.C.	M	38	L 18	L 64	L 0.7	L 0.7	L 132	L 90

R, right eye; L, left eye. Data are referred to eyes previously affected by optic neuritis.
When in one multiple sclerosis patient was tested one eye only, the fellow was not considered because his was never affected by optic neuritis, or his was excluded following the 'inclusion criteria'.

but they were still lower than the basal values. In MSWO and MSON eyes there is a similar response after photostress.

However, when comparing MSON, MSWO and control eyes we found significant differences. In MSON eyes the mean latency increase after photostress was greater than in control and MSWO eyes; this was observed considering the values obtained at 20, 40, 60 s and the average of these values (MSON vs. control: $F(1,98) = 20.04$; $P < 0.01$, MSON vs. MSWO: $F(1,86) = 25.18$; $P < 0.01$) (Fig. 2); in MSON eyes the mean percentage reduction in amplitude at the same times, was greater than in control and MSWO eyes (MSON vs. control: $F(1,98) = 30.96$, $P < 0.01$), MSON vs. MSWO: $F(1,86) = 17.19$, $P < 0.01$) (Fig. 3). In MSWO eyes the mean increase in latency and the mean percentage decrease in amplitude were similar to controls (respectively: $F(1,71) = 0.06$, $P = 0.803$, $F(1,71) = 0.72$, $P = 0.400$) (Figs. 2 and 3).

VEPs were superimposable on the basal record (RT) at 71.71 ± 4.58 s in controls and at 71.20 ± 4.66s in MSWO eyes ($F(1,23) = 0.07$; $P = 0.79$). RT observed in MSON eyes (mean 97.83 ± 5.05 s) was longer than in control ($F(1,32) = 187.29$, $P < 0.01$) and in MSWO eyes

Table 2
Mean and one standard deviation (±) of parameters of VEPs records in basal condition and 20, 40 and 60s after photostress

P100 latency (ms)			
	Controls (E = 14, S = 14)	MSWO (E = 10, S = 10)	MSON (E = 19, S = 14)
Basal	102.29 ± 2.46	105.20 ± 4.34	121.89 ± 9.28*,**
20 s	113.43 ± 3.08***	116.20 ± 4.2***	138.42 ± 8.44*,**,***
40 s	107.71 ± 3.22***	110.40 ± 3.56***	134.21 ± .71*,**,***
60 s	104.57 ± 2.77	106.80 ± 5.18	129.53 ± .79*,**,***
N75-P100 amplitude (μV)			
	Controls	MSWO	MSON
Basal	3.81 ± 1.16	3.08 ± 0.88	2.51 ± 0.95*,**
20 s	2.64 ± 1.01***	2.03 ± 0.60***	1.21 ± 0.51*,**,***
40 s	3.16 ± 1.23	2.49 ± 0.70	1.50 ± 0.41*,**,***
60 s	3.33 ± 1.21	2.70 ± 0.67	1.71 ± 0.66*,**,***

MSWO, patients with multiple sclerosis never affected by optic neuritis; MSON, patients with multiple sclerosis previously affected by optic neuritis; E, eyes tested; S, subjects tested.
*$P < 0.01$ vs. control; **$P < 0.01$ vs. MSWO; ***$P < 0.01$ vs. basal.

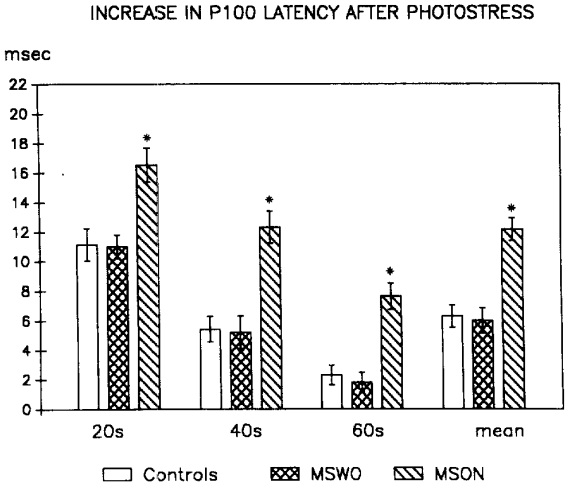

Fig. 2. Bar graphs of increase in P100 latency at 20,40,60 s after photostress. Mean: average of above. The vertical lines represent one (±) standard error. MSWO, multiple sclerosis patient without optic neuritis; MSON, multiple sclerosis patient previously affected by optic neuritis. *$P < 0.01$ vs. control and MSWO eyes by ANOVA.

(F(1,28) = 138.54; $P < 0;01$). All MSON eyes showed a longer RT than in controls and this was also observed in 3 patients with basal VEP P100 latency within normal limits (expressed as mean values of controls +3 SD; see Table 2).

3.3. PERG and FERG

PERG and FERG were carried out in controls and in those multiple sclerosis patients in whom a longer RT was observed. Since all MSWO eyes presented a RT within our normal limits, we performed these electrophysiological tests in MSON eyes only.

The mean data are presented in Figs. 4 and 5.

PERG P50 peak latency was significantly delayed in MSON eyes with respect to the control eyes ($F(1,32) = 66.82$; $P < 0.01$); the PERG P50-N95 amplitude was significantly reduced in MSON eyes when compared with control ones ($F(1,32) = 78.65$; $P < 0.01$).

FERG 2P phase was significantly delayed in MSON eyes when compared to control ones ($F(1,32) = 26.74$, $P < 0.01$); FERG 2P amplitude was significantly reduced in MSON eyes with respect to controls ($F(1.32) = 59.27$, $P < 0.01$).

No correlations between RT and PERG and FERG parameters were observed in MSON patients.

4. Discussion

The aim of our work was to evaluate the VEP after photostress response in patients with an optic nerve dysfunction. Therefore patients with multiple sclerosis previously affected by optic neuritis, but with complete recovery of visual acuity were enrolled in the study. The data obtained in these patients were compared with those of controls and with those of multiple sclerosis patients without a history of optic neuritis (MSWO).

Our results show an abnormal VEP after photostress response in MSON eyes, while in MSWO eyes a VEP after photostress response similar to control was observed.

The longer VEP recovery time after photostress observed only in MSON eyes could be ascribed to an involvement of the photoreceptors or of the inner retinal layer of the macular region, or to both (Franchi et al., 1987; Bucci et al., 1991; Parisi and Bucci, 1992; Parisi et al., 1994, 1995, 1997; Uccioli et al., 1995).

Previous studies performed by flash-ERG in multiple sclerosis patients indicate the absence of a functional impairment of the photoreceptors (Persson and Wanger, 1984; Serra et al., 1984); whereas a probable involvement of Muller glial cells occurs (Papakostopolous et al., 1989).

However, it is known that flash-ERG reflects the bioelectrical activity of the whole retina with a negligible contribution from the macular photoreceptors (Armington, 1974). A way to test the macular photoreceptors is represented by 1F response (the major component of FERG response to 30 Hz flickering light stimulation). Since previous works (Persson and Wanger, 1984; Serra et al., 1984) do not give indications that the demyelinating disease affects the sensorial retinal layers the 1F was not examined in our study as well as in a similar study (Falsini et al., 1992). A contribution to help clarify the pathological condition underlying the abnormal VEP after photostress responses observed in MSON eyes could be furnished by the evaluation of the inner retinal functionality (PERG and FERG responses).

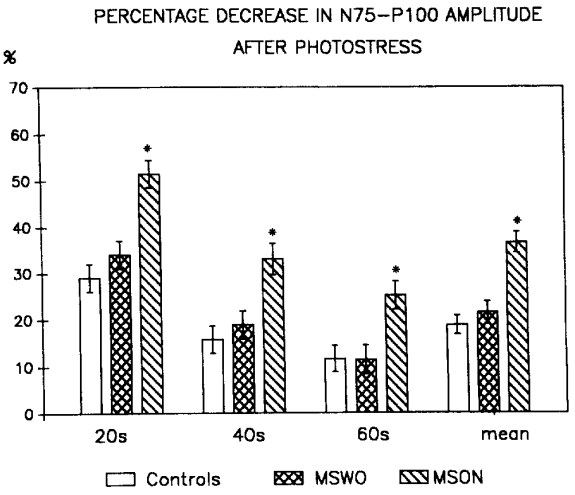

Fig. 3. Bar graphs of mean percentage decrease in N75-P100 amplitude at 20, 40 and 60 s after photostress. Mean: average of the above. The vertical lines represent (±) one standard error. *$P < 0.01$ vs. control and MSWO eyes by ANOVA.

In our MSON eyes we found both increased PERG latencies and reduced PERG amplitudes.

It is known that the PERG reflects the bioelectric activity of the innermost retinal layers. After section of the optic nerve in cats and monkeys, Maffei and Fiorentini (1981, 1982) observed a decrease in amplitude; and eventually; the disappearance of the electroretinographic signal evoked by pattern stimuli, while the electroretinographic signal evoked by flash stimuli was preserved. These electrophysiological changes were related to ganglion cells degeneration (Hollander et al., 1984; Maffei et al., 1985).

Our results are in accordance with several studies that reported an impaired PERG in multiple sclerosis patients. In fact; using transient checkerboard stimulation (Persson and Wanger, 1984; Serra et al., 1984; Celesia et al., 1986; Ryan and Arden, 1988; Holder, 1991) or steady state stimulation (Bobak et al., 1983; Plant et al., 1986) increased latencies and reduced amplitudes were respectively observed.

In addition, in MSON eyes the FERG in response to counterphased gratings stimulation was assessed. FERG in response to modulated light or to counterphased gratings stimulating a small central area (9 degrees); represent a sensitive way to test layer-by-layer the macular region function. A study performed in monkey retina suggests different sources for FERG response: 2P originates from the proximal retina; while 2F originates both in distal and proximal layers (Baker et al., 1988). Our data, in agreement with a recent report (Falsini et al., 1992), show that MSON eyes display a reduction in amplitude and a delay in phase of 2P.

Therefore, considering the data obtained by the electrophysiological investigation of the retinal function (PERG and FERG impaired responses); an impairment of the proximal retinal layers was detected in our MSON patients.

All this suggests that the delay of RT observed in MSON patients could be ascribed to an involvement of the innermost retinal layers; however, since in similar cases an impaired 2F was found (Falsini et al., 1992), a possible

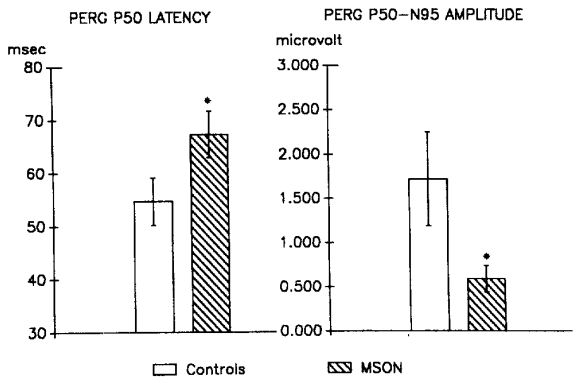

Fig. 4. Bar graphs of mean values of PERG P50 latency and PERG P50-N95 amplitude. The vertical lines represent (±) one standard deviation. *$P < 0.01$ vs. control eyes by ANOVA.

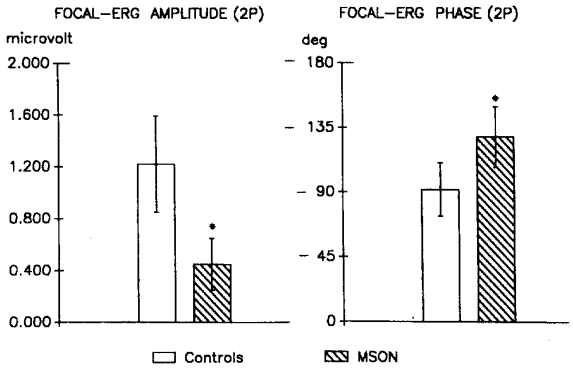

Fig. 5. Bar graphs of mean values of focal-ERG (2P) amplitude and phase. The vertical lines represent (±) one standard deviation. *$P < 0,01$ vs. control eyes by ANOVA.

contribution of the most distal retinal layers, cannot be entirely excluded.

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