Doc Ophthalmol
https://doi.org/10.1007/s10633-022-09870-2

ORIGINAL RESEARCH ARTICLE

Short-term delay in neural response with multifocal contact lens might start at the retinal level

Paulo Fernandes · Cesarina Ferreira · Joana Domingues · Ana Amorim-de-Sousa · Miguel Faria-Ribeiro · António Queirós · José M. González-Meijome

Received: 4 March 2020 / Accepted: 8 March 2022

Abstract

Introduction Multifocal simultaneous imaging challenges the visual system to process the multiple overlaps of focused and defocused images. Retinal image processing may be an important step in neuro-adaptation to multifocal optical images. Our aims are, firstly to evaluate the short-term effect of different multifocal contact lenses (MF) on retinal activity in young healthy subjects (Experiment#1) and secondly, to evaluate any changes in retinal activity in presbyopic patients fitted with MF over a 15-day period (Experiment#2).

Methods In Experiment-#1, 10 emmetropic healthy young subjects were included to evaluate the short-term effect of different MFs designs. In Experiment #2, 4 presbyopic subjects were included to wear MF for 15 days. Following the ISCEV Standards, multifocal electroretinograms (mfERGs) were recorded to evaluate different retinal regions under different conditions: with single vision contact lens (SVCL) and with center-distance and center-near MF.

Results In Exp#1 the peak time of N1, P1 and N2 were found to be delayed with the MF ($p \leq 0.040$). There was a significant reduction for N1 amplitude in all retinal regions ($p < 0.001$), while for P1 and N2 amplitudes this reduction was more significant in the peripheral regions ($p < 0.005$, ring 5 to 6). With center-near MF the mean response density (nV/deg^2) showed a significant decrease in all wave components of the mfERGs response, particularly from Ring 3 to Ring 6 ($p < 0.001$, all Rings). In Exp#2, the mean mfERG response is similar between SVCL and center-distance MF, while center-near MF showed an increase in implicit time N1 and P1 on day 1 that tends to recover to baseline values after 15 days of MF wear.

Conclusions significant changes in the mfERGs responses were found with the MF lens, being most noticeable with the center-near MF lens design. The present results suggest that the observed delay in cortical response described during the adaptation to multifocality may partially begin at the retina level.

Keywords Multifocal Contact Lenses · Multifocal Electroretinogram

Introduction

Multifocal simultaneous imaging optical solutions, challenge the visual system to take advantage of the multiple overlaps of focused and defocused images on the retina, while being able to enhance attention to a set of objects located at a specific distance of interest

P. Fernandes (✉) · C. Ferreira · J. Domingues · A. Amorim-de-Sousa · M. Faria-Ribeiro · A. Queirós · J. M. González-Meijome
Clinical & Experimental Optometry Research Lab (CEORLab), Physics Center of Minho and Porto Universities (CF-UM-UP), University of Minho, 4710-057 Gualtar Braga, Portugal
e-mail: pfernandes@fisica.uminho.pt

Published online: 02 April 2022

[1]. There are several methods that allow vision scientists and lens designers to gauge the optical performance of simultaneous image multifocal correction. These methods include schematic optical modeling using advanced ray tracing software and in vitro testing of lenses on a bench-top, life-sized physical eye model, visual simulators based on different active optical elements, and by retinal image quality metrics to quantify the visual performance in the human eye [2]. At the same time, visual simulation techniques have been developed to give patients the visual experience of a multifocal correction before applying it to the eye, helping eye care practitioners to select the most appropriate multifocal solution for each patient [3–6].

However, other aspects that involve the perceptual process of these superimposed images and the mechanisms beyond adaptation to multifocality, have not yet been fully elucidated. Data obtained with functional magnetic resonance imaging showed the existence of a neuroadaptative process in multifocality, that leads to the recruitment of different areas of the brain to deal with simultaneously focused images [7, 8]. It is recognized that these adaptive mechanisms depend on specialized neural processes, and is a time-consuming process that depends on individual factors such as age, the type of optical solution, optical power profile, some of them predictable while others are unknown. [5, 6]

There is growing interest in objectively measure the electrophysiological response of the visual system [9–12] when defocused images are presented to the eye by multifocal optics, such as multifocal contact lenses (MF) or intraocular lenses (IOL), used for myopia control [9] or for presbyopia correction [5–7, 10, 11]. Previous studies have reported a signal-dependent change in multifocal electroretinogram (mfERG) with short-term optical defocus. [7] The retina appears to be less sensitive to negative defocus than to positive defocus in myopic eyes [9] and the effects of peripheral myopic defocus on inhibition eye growth can be enhanced with topical medication. . [13, 14].

Multifocal contact lenses can be manufactured with different optical designs and can be easily exchanged, making them good solutions to change the quality of the image formed on the retina and to evaluate their repercussions in the retina or in the visual cortex. [15, 16].

Visual electrophysiology, is sensitive to changes in stimulus size, color, luminance, spatial and temporal frequency, contrast, among others [17, 18]. Simultaneous image multifocal optics reduce contrast by distributing the light across different focal lengths [19, 20] and, in eyes fitted or implanted with such optical corrections, the result in image shaping is attenuated by the out-of-focus light that is refracted or diffracted to focal planes other than the one of interest [6, 21]. However, between optical image formation and cortical perception, image processing at the retinal level is also an aspect that may deserve attention, since it is the first step in the neural processing of visual information. To date, it is unclear whether the inability to adapt to multifocality has a physical or a neural origin, or whether they are combined.

The present study assumes the hypothesis that MF can induce measurable changes in electrical activity recorded at different areas of the retina with mfERG. This may be the first evidence that the previously reported delay in neural response, measured with visual evoked potentials [15], may start in the retina.

The first goal of the present study was to evaluate the short-term effect of different MF designs on retinal responses of young healthy subjects. The use of center-distance and center-near MF refractive designs is because they are the most common principles of simultaneous vision used for MF contact lenses. The second goal was to evaluate the changes in the retinal activity in presbyopic patients wearing MF contact lenses during a 15-day period of MF wear.

Material and methods

Subjects and study design

In Experiment #1, 10 emmetropic right eyes (mean SE = 0.13 ± 0.36 D, range -0.50 to + 0.50 D) of 10 healthy subjects with a mean age of 23.4 ± 2.1 years were included. All had logMAR visual acuity of 0.00 (6/6) or better, astigmatism less than 1.00 Diopter (D), normal color vision and ocular health. Exclusion criteria included any ocular pathology, media opacity, systemic diseases, history of epilepsy, or taking medication that may interfere with or contraindicate contact lens wear.

In Experiment #2 five presbyopic subjects (mean SE OD = 1.20 ± 0.78 D; OE = 1.15 ± 0.58

D, mean Add = 2.10 ± 0.14 D) aged 51 to 54 (mean = 53.4 ± 1.8 years) were enrolled to wear monthly disposable MF during 15 days (Table 1). One subject was excluded due to attention problems and only the data for the remaining four subjects were included.

After detailed explanation of the study, all subjects (Experiment #1 and #2) gave their informed consent. This study adhered to the tenets of the Declaration of Helsinki and was reviewed and approved by the Ethics Subcommittee for Health and Life Sciences of the University of Minho.

Contact lens

Soft contact lens of the same material (Comfilcon A, Cooper Vision, Fairport, NY) were used in both Experiments (#1 and #2). Multifocal and single-vison monofocal CL were matched for material (Comfilcon A, Cooper Vision, Fairport, NY), water content of 48%, diameter of 14.0 mm and base curve of 8.60 mm. A previous evaluation with this CL material in situ showed only minor variations in P1 implicit time of the mfERG when compared with naked eye [22]. In the current study, this may indicate that the optical design, rather than the material itself, may be responsible for any changes that are observed in the mfERG response. In both experiments (#1 and #2), two MF designs were used (Fig. 1A) that yield different focal planes (Fig. 1B). The center-distance design (MFD) which uses aspherical optics to yield a central zone (2.3-mm in diameter) of constant power for distance vision, surrounded by two annular zones of increasing power at 5.0-mm and an 8.5-mm and the center-near design (MFN) which comprises a 1.7-mm central zone of constant power for near vision, surround by a 5.0-mm and an 8.5-mm annular zone of decreasing power. For the baseline control, a single-vision aspheric contact lens (SVCL) was used for both of the experiments**.**

In experiment#1, five different CL were placed, in random order, in each subject´s right eye: (1) Single vision CL as control (SVCL); (2) MFD with Add = 1.50D (MFD15) and (3) MFD with Add = 2.50D (MFD25); (4) MFN with Add = 1.50D (MFN15) and (5) MFN with Add = 2.50D (MFN25). Single vision CL and MF were matched with the same distance power (plano at distance) and all participants achieved high contrast distance VA of 0.0 LogMar or better with both type of CL (plano single vision and distance-plano MF).

In the Experiment #2, two types of CL were used: a SVCL with the appropriate distance power correction as the baseline/control and a multifocal (MFD and MFN design) with the corresponding Add power. After a comprehensive ophthalmic examination, the dominant eye was assessed by the sensory method [24] and patients were prescribed such that in the dominant eye they wore a MFD lens and one MFN lens in the non-dominant eye during 15 consecutive days.

Multifocal ERG stimulation

Multifocal electroretinograms (mfERGs) were recorded with the RETI-port/scan21 (Roland Consult, Wiesbaden, Germany), following the Standards of the International Society for Clinical Electrophysiology of Vision (ISCEV) [23]. The stimulus array consisted of 103 hexagonal elements scaled with a distortion and eccentricity factor of 4.0, displayed randomly on a TFT monitor (frame rate of 60 Hz) at a distance of 28 cm, covering a field of view of approximately 50°. Each hexagon was temporally modulated between black (luminance = 1.47 ± 0.06 cd/m2) and white (luminance = 220.32 ± 1.23 cd/m2) according to a pseudorandom binary m-sequence comprising 2

Table 1 Demographic and refractive data of the subjects enrolled in experiment #2

Patient	Gender	Age (years)	Refraction		
			OD (D)	OS (D)	Add (D)
1	Female	52	+0.75–0.50×90	+1.00–0.50×75	2.25
2	Female	51	+1.75	+1.75	2.25
3	Female	55	+2.25	+1.75	2.00
4	Female	55	+0.50	+0.50	2.00
5	Female	54	+1.00	+1.00–0.25×130	2.00

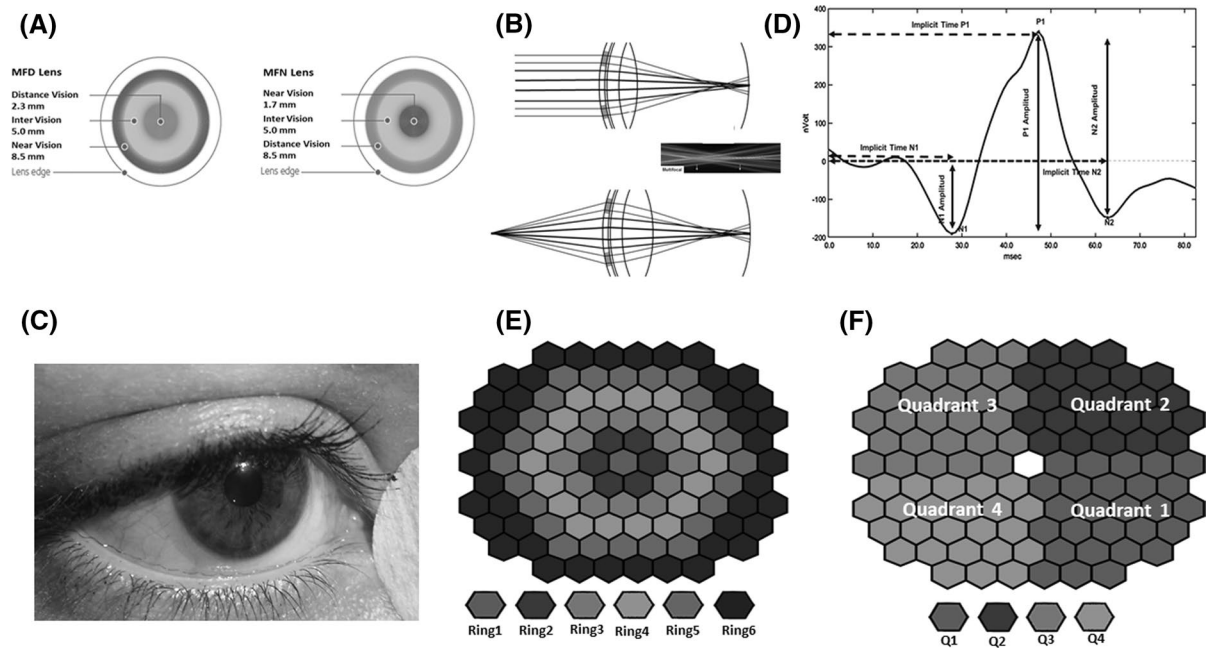

Fig. 1 Multifocal center distance and center-near design (**A**). **B** A schematic drawing of the different focal planes of the multifocal lenses and a simulation of light distribution on the retina. **C** DTL electrode over the contact lens. **D** typical waveform of the mfERG obtained for each evaluated area, with three elements of the first order kernel (N1, P1 and N2)—Peak time (ms), Amplitude (nV). The influence of de multifocal contact lens was evaluated in (**E**) 6 concentric (Ring 1 to Ring 6) and (**F**) 4 retina quadrants (Q1 = nasal inferior; Q2 = nasal superior; Q3 = temporal superior; Q4 = temporal inferior)

[13]–1 steps using on/off with a probability of 50%. The mean display luminance was approximately 120 cd/m [2]. 12 cycles (47 s each) were obtained to achieve an average of 10% artefact rejection. Recordings were amplified (range, 100 μV) and automatically bandpass filtered (filter range 10–100 Hz).

Multifocal ERG recording

Before placing the electrodes, the skin was cleansed with an abrasive gel, the gold-cup reference and ground electrodes were placed 10 mm lateral to the outer canthus of the tested eye and on the central forehead, respectively. In both Experiments, subjects were light-adapted for 10 min and mfERG performed monocularly using a DTL-plus electrode (Dawson-Trick-Litzkow) placed onto the lower fornix and in contact with the anterior surface of the CL (Fig. 1C). [22] For CL replacement, the CL was replaced with the DTL in the eye and with a minimum level of discomfort, the impedance was checked and the DTL replaced if the impedance was > 5 kOhm.

In experiment #1, the pupil was previously fully dilated with 1% Pheniliphrine (Davinefrina, DÁVI II) and the subjects were instructed to fixate a red cross in the center of the stimulation screen. For baseline measurements with the SVCL and with the MFD the participants were optically compensated for the 28 cm distance with + 3.00 D additional lens, the fixation was monitored with the system´s built-in camera and impedance levels checked before each measurement. Recordings began immediately after 15 min of CL adaptation and took approximately 10 min to complete each set of mfERG recordings for each particular CL condition. A 15-min washout period was taken before the start of the next MF measurement, making a total of about 110 min of measurement time for each subject.

In experiment #2, baseline measures were recorded with an SVCL fitted in both eyes with each subject´s distance correction, followed by measurements with the MF lens fitted according the manufacturer´s guide and after a 15 min of lens adaptation. To ensure the same amount of defocus in both eyes and the same focal plane with the MF at the level of stimulus plane,

participants were optically corrected for central vision at a viewing distance of 28 cm. In the case of SVCL with a + 3.00 D lens, while for the MF with the additional optical correction so that each eye achieved the same visual acuity (1.0) for the viewing distance of the mfERG stimulus. With the MFD lens, this value averaged + 2.00 D (range + 1.00 to + 3.00) while withr the MFN lens it averaged + 1.25 D (range + 1.00 to + 2.00). All mfERGs were obtained monocularly and repeated after 15 days of MF wear. All recommendations regarding compliance, care, use and handling were carefully given. Subjects were instructed to wear the MF at least 8 h per day and the 15-day measurements were not taken until the 15 consecutive days of lens wear had been completed.

In order to work under normal physiological conditions of pupil size, which is a critical factor in determining MF lens performance, mfERGs were performed under non-dilated conditions. During recordings, any possibility of artefacts such as eye movements, head tilt, poor fixation or poor electrode contact were carefully monitored.

Data analysis

The first-order kernel response (Fig. 1D) was extracted and the conventional mfERG wave components N1, P1 and N2 were evaluated (amplitude in nV, implicit time in ms) according to ISCEV Standards [23]. Briefly, the amplitude of N1 was measured from the light stimulus onset (0 ms) to the trough of the first negative wave; P1 amplitude was measured from the trough of the N1 wave to the peak of the positive P1-wave while N2 amplitude was measured from the trough of the P1 wave to the peak of the negative N2-wave. The temporal properties of the mfERG response, usually defined by the time-to-peak (implicit time), measured from stimulus onset to the peak of the N1, P1 and N2 components. The scaled density regional (in nV/deg [2]), which reflect the regional amplitude for the correct angular size of each hexagon, was also evaluated. The 103 hexagonal elements were grouped into six concentric rings: a central hexagon corresponding to the foveal region (Ring 1 subtended 3.61 degrees, eccentricity 0) and five concentric rings at different eccentricities corresponding to the parafoveal, perifovea and more peripheral region: Ring 2 (3.13–10.85 degrees), Ring 3 (10.85–20.63 degrees), Ring 4 (20.63–32.46 degrees), Ring 5 (32.46–46.36 degrees) and Ring 6 (39.78–58.9 degrees) (Fig. 1E). Quadrants 1 to 4 (Q1 to Q4) correspond to the inferior right retina, superior right retina, superior left retina and inferior left retina, respectively (Fig. 1F).

Statistical analysis was conducted using SPSS v21.0 (IBM Inc. IL). The normality of the data distribution was assessed with the Shapiro–Wilk test. The effect of MF design with different Add on the different peaks (N1, P1 and N2 for implicit time and amplitude and in each region of the retina), was analyzed using a 5 factor (baseline, MFD15, MFD25,MFN15, MFN25) one-way repeated measures analysis of variance (one-way -ANOVA) (normally distributed) or Friedman-test (non-normally distributed). Post hoc tests with Bonferroni adjustment were used to analyze the level of significance due to multiple comparisons/interactions effects. The level of statistical significance was set at $p < 0.05$.

Results

Experiment #1- The results for the different components of the mfERG wave (N1, P1and N2) in the different regions of the retina and for the five different conditions, are graphically represented in Fig. 2 (implicit time) and in Fig. 3 (amplitude). The regional response density (nV/deg [2]) is shown in Table 2

Implicit times

For the total mfERG signal, the mean N1 peak time values were 24.99 ± 0.78 ms, 30.93 ± 2.01 ms, 29.83 ± 2.91 ms, 30.08 ± 3.31 ms and 30.34 ± 2.65 ms for SVCL, MFD15, MFD25, MFDN15 and MFN25, respectively. The mean values of P1 peak time were 45.20 ± 1.14 ms, 49.71 ± 1.56 ms, 49.15 ± 2.42 ms, 49.39 ± 2.62 ms and 49.51 ± 1.90 ms for SVCL, MFD15, MFD25, MFDN15 and MFN25, respectively, while for N2 were 62.86 ± 5.25 ms, 69.21 ± 3.08 ms, 68.84 ± 5.96 ms, 70.51 ± 5.59 ms and 69.45 ± 4.36, respectively. When compared with SVCL, all MF designs showed a significant increase of approximately 5 ms in both N1 time (Fig. 2A) and P1 time (Fig. 2B) in all retina regions (Ring 1 to Ring 6, $p = 0.001$, Friedman-test, $W = 0.3$), except for N1 where the differences are significant only with the

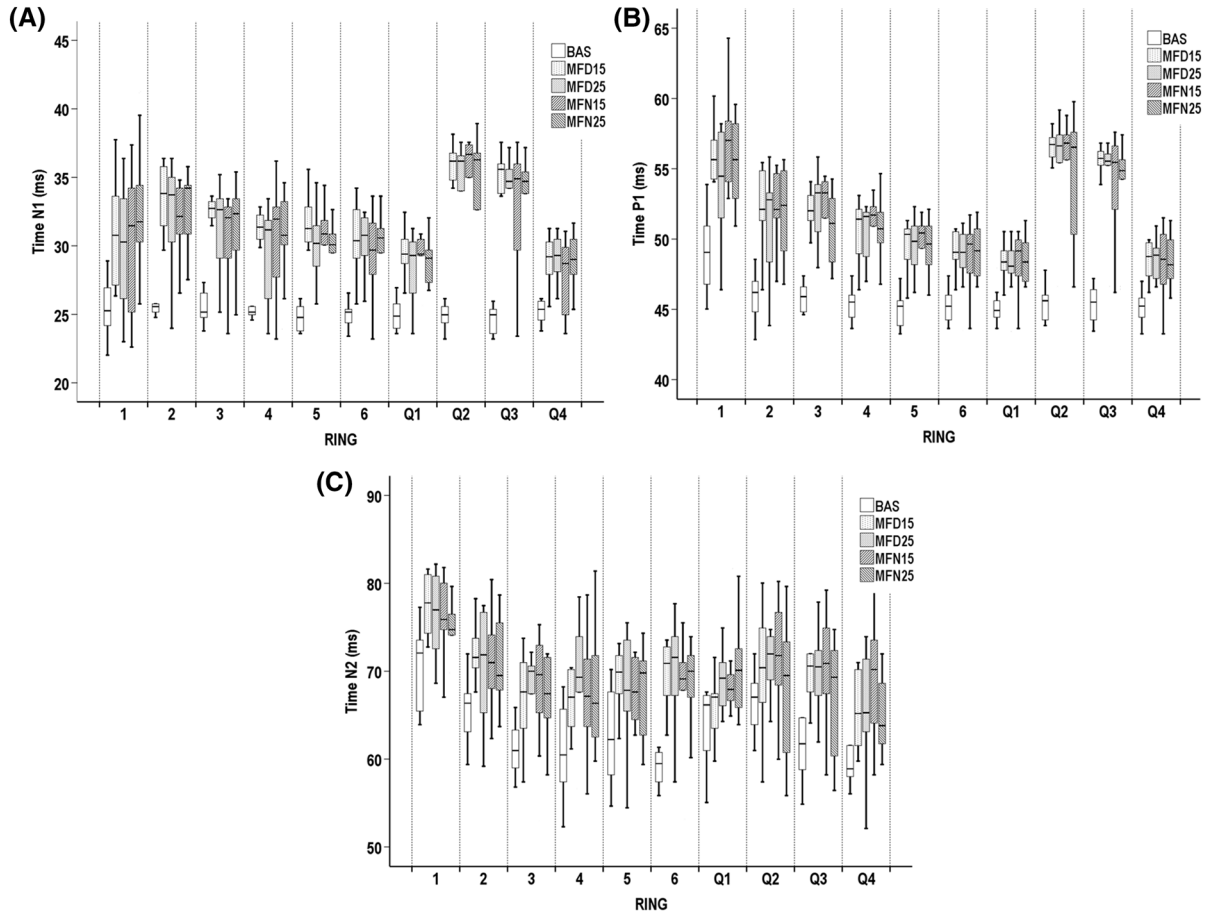

Fig. 2 Experiment #1—Boxplot distribution of N1 (**A**), P1 (**B**) and N2 (**C**) of the mfERG response for the five conditions evaluated. Compared with baseline, all MF showed a significant increase in all peak times in all mfERG rings and with greater evidence in superior retina. *Bas* baseline with single vision CL, *MFD*15 multifocal contact lens "center-distance" design Add 1.50, *MFD*25 multifocal contact lens "center-distance" design Add 2.50, *MFN*15 multifocal contact lens "center-near" design Add 1.50, *MFN*25 multifocal contact lens "center-near" design Add 2.50

MFN25 design in Ring 1 ($p = 0.004$, ANOVA Eta Squared = 0.2;). On the other hand, the increase in N2 peak time (Fig. 2C) was significant in central regions (Ring 1 and Ring2), in particular with MFD15 and MFD25 ($p \leq 0.04$, ANOVA Eta Squared = 0.1 with both MFD designs). In the analysis by quadrants, there is also a significant increase in N1 and P1 peak implicit time in all the four quadrants when compared to SVCL, particularly for the superior retina (Q2, and Q3, $p = 0.001$, Friedman test, $W = 0.3$). For N2 peak time there is also an increase, most significantly with MFN design, in the inferior retina in quadrants Q1 ($p = 0.001$, Friedman test, $W = 0.4$) and Q4 ($p = 0.038$, ANOVA, Eta Squared = 0.4).

Response amplitude

In experiment #1**,** for the total mfERG response, the mean values of N1 peak amplitude were 204.10 ± 50.92 nV, 122.27 ± 31.72 nV, 149.66 ± 37.97nV, 138.56 ± 37.83n V and 138.12 ± 33.36 nV for SVCL, MFD15, MFD25, MFDN15 and MFN25, respectively. The mean values of P1 peak amplitude were 587.34 ± 102.86 nV, 396.21 ± 80.73 nV, 438.44 ± 66.31 nV, 435.47 ± 78.86 nV and 419.91 ± 82.93 nV for SVCL, MFD15, MFD25, MFDN15 and MFN25, respectively, while for N2 they were 492.98 ± 87.97 nV, 354.51 ± 78.94 nV, 405.44 ± 58.07 nV, 391.01 ± 69.12 nV and 357.03 ± 82.66 nV, respectively (Fig. 3A–C). The

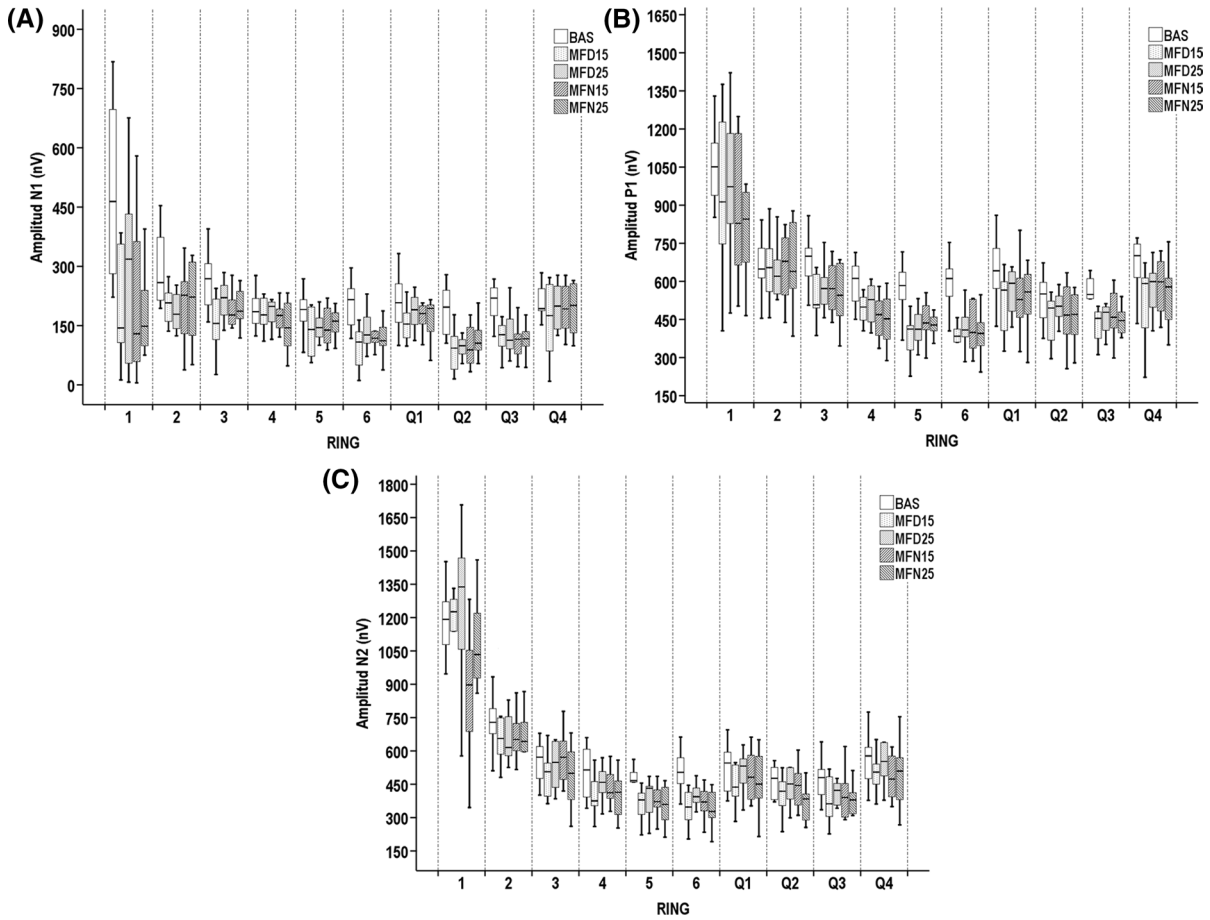

Fig. 3 Experiment #1—Boxplot distribution of N1 (**A**), P1(**B**) and N2(**C**) absolute peak amplitude of the mfERG response for the five conditions evaluated. Overall, there is a decrease in all peak amplitudes with all MF designs, especially at central and more peripheral regions, when compared to baseline. *Bas* baseline with single vision CL, *MFD*15 multifocal contact lens "center-distance" design Add 1.50, *MFD*25 multifocal contact lens "center-distance" design Add 2.50, *MFN*15 multifocal contact lens "center-near" design Add 1.50, *MFN*25 multifocal contact lens "center-near" design Add 2.50

mean response density (nV/deg [2]) for all the retina regions is showed in Table 2. Regional analysis revealed a significant decrease for N1 in Ring 1 ($p=0.019$, ANOVA, Eta Squared = 0.2), Ring 3 ($p=0.002$, ANOVA, Eta Squared = 0.3),) and Ring 6 ($p<0.001$, ANOVA, Eta Squared = 0.4) and this decrease is more evident with the MFD15, MFN15 and MFN25 lenses. For the P1 peak there is also a decrease in all retinal regions being significant in the more peripheral regions (Ring 3 to Ring 6) and with the MFN designs ($p<0.03$, ANOVA, Eta Squared = 0.4, for both MFN designs). For the N2 component, the decreased in amplitude is only significant in the peripheral rings specifically in Ring 5 with MFN25 ($p=0.011$ ANOVA, Eta Squared = 0.6,) and Ring 6 with all MF designs ($p<0.001$, ANOVA, Eta Squared = 0.2). For analysis by quadrants there is also a decrease in N1 peak amplitude which is significant in Q2 and Q3 ($p<0.001$, Friedman test, $W=0.3$, for all MF designs), while for P1 the decrease is significant only for Q3 and with MFN25 design ($p=0.015$, ANOVA, Eta Squared = 0.3).

For Experiment #2 the average mfERG response curve of the 4 subjects and for each ring, is shown in Fig. 4A for the MFD lens of the dominant eye and in Fig. 4B for the MFN lens of the non-dominant eye. The mean peak implicit time for N1 and P1 of the mfERG Rings is shown in Table 3 and for quadrants is shown in Table 4. By looking at the shape of the curve, in the dominant eye, similar results are found

Table 2 Experiment #1: Mean values and ± SD of response density (nV/deg^2) for N1, P1 and N2 peak of mfERG response for each retinal location in the 5 conditions: baseline with single vision CL–B; *MFD*15 multifocal contact lens–L1 "center-distance" design Add 1.50; *MFD*25 multifocal contact lens "center-distance" design Add 2.50–L2; *MFN*15 multifocal contact lens "center-near" design Add 1.50–L3; *MFN*25 multifocal contact lens "center-near" design Add 2.50)–L4

Amplitude (nV/deg^2)		Baseline (B)	MFD15 (L1)	MFD25 (L2)	MFN15 (L3)	MFN25 (L4)	*p*	*Post-hoc test*
N1	Sum	7.37 ± 1.84	4.42 ± 1.15	5.41 ± 1.37	5.01 ± 1.37	4.99 ± 1.21	< 0.001[p]	B-L1;B-L2;B-L3;B-L4
	Ring 1	58.91 ± 24.99	22.79 ± 16.62	34.61 ± 26.61	26.37 ± 24.70	26.38 ± 23.46	0.019[p]	B-L1;B-L3;B-L4
	Ring 2	25.35 ± 7.80	17.80 ± 4.37	16.14 ± 4.11	17.49 ± 9.09	18.70 ± 8.31	0.047[p]	ns
	Ring 3	16.79 ± 4.85	9.55 ± 4.12	13.49 ± 2.89	11.50 ± 3.97	12.26 ± 2.81	0.002[p]	B-L1;B-L3
	Ring 4	8.99 ± 2.05	8.80 ± 2.79	8.88 ± 2.52	7.76 ± 2.35	6.99 ± 3.02	0.336[p]	ns
	Ring 5	6.76 ± 1.99	4.74 ± 2.13	5.25 ± 1.22	5.42 ± 1.77	5.63 ± 1.29	< 0.130[p]	ns
	Ring 6	5.61 ± 1.53	2.71 ± 1.33	3.70 ± 1.36	3.45 ± 1.12	3.28 ± 1.15	< 0.001[p]	B-L1;B-L2;B-L3;B-L4
	Q1	7.61 ± 2.43	5.60 ± 1.50	6.75 ± 1.56	6.7 ± 2.67	6.11 ± 1.87	0.207[np]	ns
	Q2	6.97 ± 2.22	3.17 ± 1.93	3.54 ± 1.83	3.46 ± 1.73	4.12 ± 1.62	< 0.001[p]	B-L1.B-L2.B-L3.B-L4
	Q3	7.58 ± 1.68	4.41 ± 1.40	4.80 ± 2.09	3.99 ± 1.55	4.11 ± 1.60	< 0.001[p]	B-L1.B-L2.B-L3.B-L4
	Q4	7.23 ± 1.97	5.79 ± 3.14	7.15 ± 1.92	6.90 ± 2.20	6.75 ± 2.22	0.653 [p]	ns
P1	Sum	21.22 ± 3.72	14.32 ± 2.92	15.84 ± 2.40	15.73 ± 2.85	15.17 ± 3.00	< 0.001[p]	B-L1;B-L2;B-L3;B-L4
	Ring 1	121.05 ± 27.07	111.43 ± 36.63	116.24 ± 35.31	104.46 ± 31.82	100.71 ± 31.42	0.629[p]	ns
	Ring 2	58.29 ± 9.29	57.86 ± 11.56	55.87 ± 9.49	57.42 ± 11.42	57.76 ± 14.02	0.991[p]	ns
	Ring 3	42.37 ± 6.86	33.74 ± 5.58	36.07 ± 5.38	36.31 ± 6.62	34.15 ± 7.17	0.030[p]	B-L1
	Ring 4	27.52 ± 4.12	22.40 ± 3.88	24.18 ± 3.73	21.80 ± 3.85	20.92 ± 4.81	0.007[p]	B-L3;B-L4
	Ring 5	20.41 ± 4.26	13.77 ± 3.10	14.92 ± 2.40	16.14 ± 2.72	15.47 ± 2.87	< 0.001[p]	B-L1;B-L2;B-L3;B-L4
	Ring 6	16.13 ± 3.07	10.31 ± 2.21	11.54 ± 2.14	11.27 ± 2.50	10.83 ± 2.29	< 0.001[p]	B-L1;B-L2;B-L3;B-L4
	Q1	22.78 ± 4.73	18.95 ± 4.21	20.29 ± 3.18	19.19 ± 4.88	19.34 ± 4.44	0.275[p]	ns
	Q2	19.05 ± 3.47	16.26 ± 3.24	17.76 ± 3.66	17.06 ± 4.23	16.43 ± 3.44	0.426[p]	ns
	Q3	19.51 ± 2.84	15.32 ± 2.46	16.44 ± 2.02	16.92 ± 3.48	15.65 ± 3.10	0.015[p]	B-L1;B-L4
	Q4	23.53 ± 4.50	18.45 ± 5.25	20.56 ± 3.48	20.63 ± 3.81	19.94 ± 4.16	0.088[np]	ns
N2	Sum	17.81 ± 3.18	12.81 ± 2.85	14.65 ± 2.10	14.13 ± 2.50	12.90 ± 2.99	0.007[np]	B-L1;B-L3;B-L4
	Ring 1	136.33 ± 24.58	132.81 ± 30.01	148.84 ± 38.61	109.23 ± 42.74	122.13 ± 33.18	0.100[np]	ns
	Ring 2	63.02 ± 10.93	59.98 ± 13.74	57.90 ± 9.54	57.65 ± 11.82	55.60 ± 15.82	0.735[p]	ns
	Ring 3	36.50 ± 7.97	31.75 ± 6.58	33.85 ± 6.39	36.04 ± 7.14	30.57 ± 8.62	0.309[p]	ns
	Ring 4	23.62 ± 5.19	18.76 ± 4.05	21.45 ± 3.64	20.47 ± 3.60	18.74 ± 4.38	0.068[p]	ns
	Ring 5	17.20 ± 2.70	13.03 ± 2.52	14.32 ± 3.04	13.61 ± 2.87	13.14 ± 2.98	0.011[p]	B-L1;B-L4
	Ring 6	13.72 ± 2.50	9.20 ± 2.24	10.79 ± 1.76	10.10 ± 1.82	9.18 ± 2.15	< 0.001[p]	B-L1;B-L2;B-L3;B-L4
	Q1	19.13 ± 4.10	15.94 ± 3.22	18.21 ± 3.28	17.42 ± 4.00	16.39 ± 4.91	0.373[p]	ns
	Q2	16.62 ± 2.51	13.22 ± 5.38	15.81 ± 2.66	15.55 ± 3.34	12.10 ± 4.81	0.080[np]	ns
	Q3	17.05 ± 3.11	13.65 ± 3.62	14.86 ± 1.89	13.48 ± 5.83	12.50 ± 4.92	0.089[np]	ns
	Q4	20.27 ± 4.16	17.21 ± 3.76	19.05 ± 3.42	17.22 ± 3.47	17.67 ± 4.86	0.348[p]	ns

(p) ANOVA repeated measures–Bonferroni post hoc test; (np) Friedman test–Bonferroni post hoc test

ns Non-statistically significant

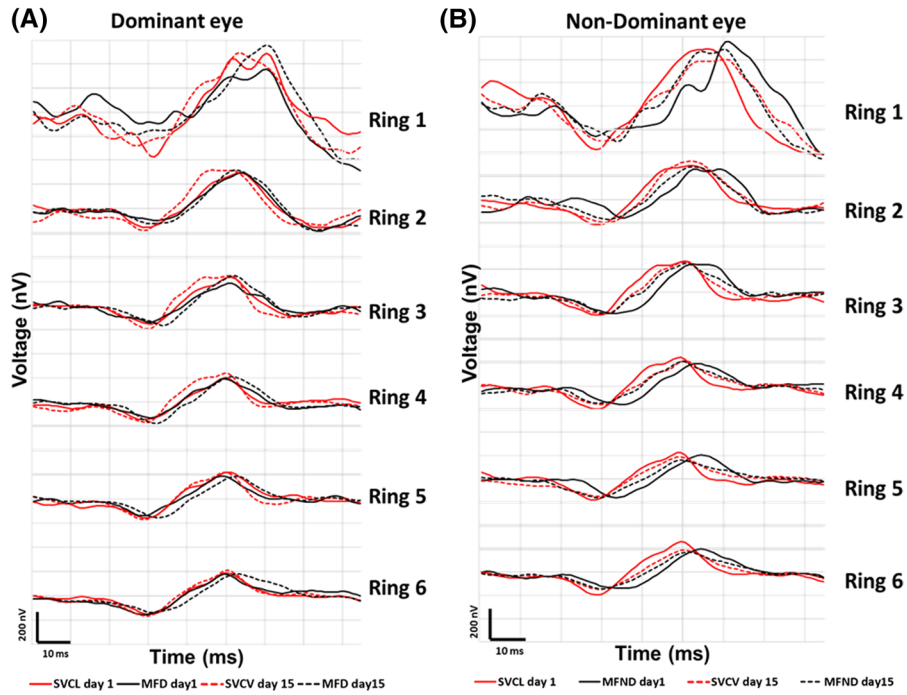

Fig. 4 Experiment #2—Mean mfERG curve response from central Ring 1 to peripheral Ring 6, in Dominant eye with MFD (**A**) and Non-Dominant eye with MFN (**B**) at day 1 (solid line) and 15 days (dashed lines) of MF wear. There is an increase in implicit time at day one with MFN lens and is reduced after 15 days and tends to be similar to SVCL at day 1. Solid lines represents de results at day 1 and dashed lines represents the results for the 15-days of lens wear. *SVCL* single vision contact lens, *MFD* center distance multifocal contact lens, *MFN* center-near multifocal contact lens

with the SVCL (red curve) and with the MFD lens (black curve), both on day 1 (solid lines) and 15-day (dashed lines) of lens wear. Despite the small variations observed in the regions bounded by ring 1 to Ring 3, in general both the amplitude and implicit time of N1 and P1 peaks are very similar between the SVCL and MF in the dominant eye, as shown in Table 3.

In contrast, in the non-dominant eye with the MFN lens there is time shift on the entire mfERG response (solid black curve) that does not persist at 15 days of lens wear (Fig. 4B). At day 1 the N1 increases by about 4 to 6 ms (ms) with the MFN lens when compared with the SVCL lens, however this difference decreases to 1 to 2 ms at day 15. This increase at day 1 and decrease at day 15 is very similar in all the retinal regions (Ring 1 to Ring 6) as shown in Table 3. Similar results are found for the P1 time, with an increase with the MFN lens on day 1 of about 5 ms, which decreases to 2 ms after the 15 days of lens wear. After 15 days of MFN lens wear, the N1 and P1 peak time shows very similar values to those obtained with the SVCL on day 1 (Table 3).

For the different regions of the retina analyzed by quadrants, the results for the mean mfERG curve are shown in Fig. 5A for dominant eye and Fig. 5B for Non-dominant eye and the mean values of the implicit peak times N1 and P1 are shown in Table 3. The results also show that there is a delay of the entire mfERG curve on day 1 with the MFN lens and an increase in both N1 and P1 time that is reduced considerably on day 15 (Fig. 5B). In the inferior retina (Q1 and Q4) the increase in N1 and P1 was to 4 ms on day 1 that decreased to about 2 ms on day 15. For the upper retina (Q2 and Q3), on day 1 the increase was much higher, about 8 to 11 ms in either N1 or P1 which decreased to approximately 3 ms on day 15 (Table 3). The SVCL showed no such a trend and with the MFD lens in the dominant eye there was no significant change in either amplitude or implicit time.

The difference for the different individuals at day 1 and day 15 of the N1 and P1 implicit time are shown in Table 4. The values were obtained by subtracting the value of day 15 from the value of day 1 and a positive value means an increase in time from day 1 to day 15, while a negative value means a decrease in time from day 1 to day 15. In all subjects and all retinal regions, with the MF lens the changes are higher and this difference is even higher with the MFN lens, especially at time N1, despite some variability.

Table 3 Experiment #2: Mean differences and standard error of the mean (SEM)) for the N1 and P1 implicit time (in milliseconds) of the mfERG response by Rings and Quadrants for Dominant and Non-Dominant eye at day 1 and 15-day

		SVCL								MF							
		Dominant eye				Non-Dominant eye				Dominant eye—MFD				Non-Dominant eye—MFN			
		Day 1		Day 15		Day 1		Day 15		Day 1		Day 15		Day 1		Day 15	
		Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Ring 1	N1	29.1	0.6	31.7	1.2	29.1	1.3	30.2	2.3	31.3	0.7	29.8	6.0	33.6	4.0	29.7	3.3
	P1	51.6	2.1	52.6	0.4	51.3	2.7	52.0	3.9	57.9	3.1	56.4	2.5	60.9	0.3	57.5	2.9
Ring 2	N1	29.9	3.2	29.5	2.0	27.8	1.1	29.4	1.4	33.7	2.5	31.4	2.5	34.3	0.1	30.4	50.6
	P1	51.1	1.4	50.1	0.8	51.9	0.9	50.4	1.1	52.3	1.8	51.8	1.1	53.0	1.3	51.2	0.3
Ring 3	N1	30.7	2.5	30.7	1.9	28.4	0.9	29.0	0.8	30.6	5.7	33.2	2.0	32.7	2.5	31.0	1.9
	P1	49.7	2.5	49.9	0.8	45.4	3.1	46.5	4.2	53.1	3.8	53.0	2.2	49.7	6.6	51.0	4.9
Ring 4	N1	30.2	2.5	29.5	0.8	28.2	1.2	28.0	0.3	31.4	1.8	31.2	2.5	34.4	0.8	29.5	1.2
	P1	49.3	1.8	50.1	2.2	48.4	0.9	49.1	0.9	52.7	1.6	51.8	1.2	53.0	1.8	50.1	1.1
Ring 5	N1	29.2	1.3	29.4	1.2	26.7	0.8	27.7	0.7	29.6	1.6	31.4	1.4	32.9	0.6	29.1	1.1
	P1	50.4	1.0	49.9	1.5	48.3	0.8	47.4	1.1	51.1	2.6	52.0	0.9	54.3	3.0	49.4	2.0
Ring 6	N1	30.1	1.7	30.1	1.8	28.2	1.1	27.8	0.8	31.0	2.8	31.5	2.3	36.4	1.4	31.2	3.0
	P1	50.4	1.8	50.4	1.5	49.9	2.0	47.7	1.4	51.4	3.5	51.6	1.3	55.2	1.2	51.0	2.2
Q1	N1	28.4	1.0	28.7	1.1	28.1	1.5	27.6	0.8	32.3	5.3	34.0	4.8	32.1	2.9	30.5	1.2
	P1	50.8	3.3	51.7	4.3	50.2	2.0	48.7	0.7	53.6	5.9	54.9	4.6	54.3	3.8	59.0	1.8
Q2	N1	28.0	2.0	28.0	0.6	27.8	1.1	27.3	0.4	33.2	3.9	33.1	4.4	39.4	0.5	28.3	1.0
	P1	51.9	3.6	51.5	4.0	49.0	1.7	47.7	1.2	52.3	6.1	53.2	3.6	60.7	1.3	51.4	3.5
Q3	N1	29.5	1.4	30.4	0.7	29.7	2.4	28.7	1.5	32.2	2.9	32.3	1.0	37.8	1.1	29.1	1.5
	P1	49.6	1.0	50.9	1.5	48.8	0.6	49.5	1.5	51.9	2.2	52.1	0.9	58.8	5.4	50.4	2.9
Q4	N1	28.1	3.8	29.1	1.8	28.5	1.6	27.9	0.4	30.6	2.2	31.3	0.4	31.5	1.8	29.7	0.7
	P1	48.8	1.5	50.4	1.6	49.1	1.3	49.1	1.4	52.3	3.2	51.4	0.5	51.7	2.1	50.6	2.9

SVL single vision contact lens, *MFD* center-distance multifocal contact lenses, *MFN* center-near multifocal contact lenses, *Q* Quadrant

Discussion

In an attempt to understand whether the defocus adaptation is entirely a cortical processor whether it involves processes in the retina, two experiments were performed in this study. One to understand whether the retina is sensitive to defocus induced by MF contact lenses of different geometries and the other to study the retinal response during the MF adaptation process. From the results found, both the response amplitude and implicit time of mfERG, both change with the induction of different level of defocus. The changes observed in amplitude and delay in time are very similar with the different MF designs. On the other hand, it appears that the changes observed in implicit time tend to decrease with MF adaptation over time, which may suggest a change in retinal pathway activity in response to contrast changes due to the multifocality effect**.**

Previous studies have shown that optical defocus produces a small reduction in central macular mfERG response [26] and a signal-dependent change to short-term imposed optical defocus [9]. It appears that the retina has a decoding system, probably located in the near peripheral retina and in innermost layers, that is especially tuned to low spatial frequencies [27] and is able to differentiate between positive and negative defocus signals. This in some way may explain the results observed in the present study, where a reduction in amplitude and time delay of the mfERG response was found with both MF designs, as seen in experiment #1. These changes are most significant in the central and

Table 4 Experiment #2: Difference of the N1 and P1 implicit time (in milliseconds) values between day1 and day15 for individual subject and for Dominant and Non-Dominant eye

		Subject 1				Subject 2				Subject 3				Subject 4			
		D eye		ND eye		D eye		ND eye		D eye		ND eye		D eye		ND eye	
		SVCL	MFD	SVCL	MFN	SVCL	MFD	SVCL	MFN	SVCL	MFD	SVCL	MFN	SVCL	MFD	SVCL	MFN
Ring 1	N1	2.9	−4.7	−2.7	−6.5	0.2	−12.7	2.9	−5.6	2.6	0.8	6.3	1.5	4.7	6.5	−2.1	−4.9
	P1	−0.9	7.9	5.3	9.0	−1.6	6.3	−9.4	0.4	0.8	−2.6	−5.1	0.6	5.7	−5.7	6.5	3.3
Ring 2	N1	1.4	−10.4	3.5	−5.5	−4.3	−3.4	0.4	−3.0	5.3	−0.6	2.2	−2.7	−3.9	5.3	0.2	−4.5
	P1	−1.9	3.5	0.9	4.4	−1.9	−1.0	4.3	2.7	2.4	−0.2	1.1	1.4	−2.5	−0.2	−0.2	1.2
Ring 3	N1	0.0	−8.6	−0.6	−4.1	−2.9	13.2	1.4	−0.2	8.3	−1.4	0.6	−0.6	−5.5	7.3	0.8	−2.0
	P1	4.9	7.1	0.6	11.6	−2.9	2.8	−5.1	−14.5	1.0	−7.7	−0.6	−10.4	−2.2	−2.0	0.4	8.1
Ring 4	N1	0.2	−6.5	−0.6	−5.1	−3.5	−1.4	−2.4	−3.1	4.7	0.0	1.6	−4.8	−4.1	6.9	0.4	−6.6
	P1	0.6	4.7	−1.4	8.3	1.8	1.4	−0.8	0.3	6.9	−0.2	−0.2	−0.1	−6.1	−2.7	−0.4	3.1
Ring 5	N1	0.2	−0.9	2.2	−5.1	0.8	2.6	2.2	−2.5	4.7	−1.0	1.0	−1.7	−4.7	6.5	−1.2	−6.1
	P1	−0.4	5.3	−0.2	6.3	0.8	−2.1	2.0	7.2	2.7	−0.8	−0.6	−0.8	−5.3	−5.7	2.3	6.9
Ring 6	N1	−0.8	−5.7	1.6	−7.9	−1.6	−0.2	−3.5	−3.3	6.5	1.8	0.4	−3.9	−4.1	6.1	−0.2	−5.9
	P1	0.8	8.4	0.0	4.3	−2.6	−2.9	8.6	3.0	5.7	−0.6	−0.6	3.3	−4.1	−5.9	0.8	5.9
Q1	N1	0.2	−8.5	1.6	−6.8	0.4	3.5	−4.1	1.5	0.4	0.8	1.0	3.4	0.2	11.0	−0.6	−4.8
	P1	0.8	11.6	1.6	−0.2	0.0	−4.1	4.1	−9.8	13.0	−1.0	−1.0	−10.2	−10.0	−11.6	1.4	1.6
Q2	N1	0.8	−9.2	1.0	−10.4	−3.3	−0.6	−2.8	−10.3	1.2	0.4	0.0	−10.4	1.3	9.3	0.0	−13.6
	P1	0.2	10.2	−1.4	12.0	−3.5	−5.9	6.7	7.4	12.0	−0.2	−0.8	5.8	−10.2	−8.1	0.6	12.1
Q3	N1	−1.0	−4.3	0.0	−10.7	0.0	−1.2	−3.9	−8.7	4.5	0.8	1.2	−5.7	−0.1	4.9	−1.4	−9.9
	P1	0.2	4.5	0.4	6.3	0.4	0.0	−3.5	9.8	5.9	−0.8	−0.2	11.8	−1.6	−4.7	0.6	5.3
Q4	N1	−0.8	−4.3	0.8	−2.9	−7.3	2.7	−4.3	0.5	4.9	0.8	1.2	0.5	7.3	3.7	0.0	−5.3
	P1	1.6	3.9	−0.6	5.1	3.7	4.9	0.4	−3.9	5.1	−1.4	0.0	−2.0	−3.9	−3.7	0.4	5.1

The values were obtained by subtracting the value of day 15 from the value of day 1. A positive value means an increase in time from day 1 to day 15, while a negative value means a decrease in time from day 1 to day 15

D Dominant eye, *ND* Non Dominant eye, *Q* Quadrant, *SVCL* single vision contact lens, *MFD* center-distance multifocal contact lenses, *MFN* center-near multifocal contact lenses

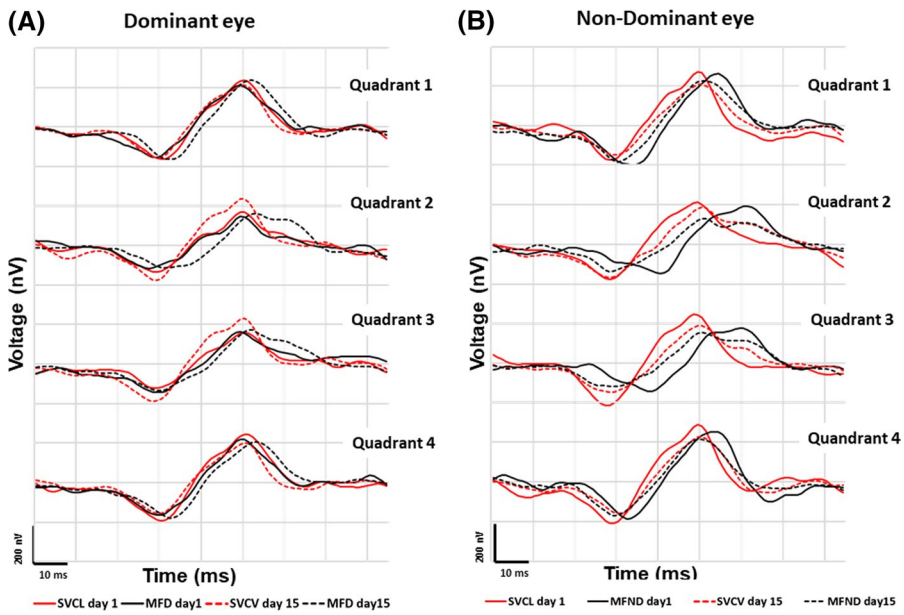

Fig. 5 Experiment #2—Mean mfERG curve response for different quadrants, in Dominant eye with MFD (**A**) and Non-Dominant eye with MFN (**B**) at day 1 (solid line) and 15 days (dashed lines) of MF wear. There is an increase in implicit time at day one with MFN lens, being most significant in the superior retina, and is reduced after 15 days. Solid lines represents de results at day 1 and dashed lines represents the results for the 15-days of lens wear. *SVCL* single vision contact lens, *MFD* center distance multifocal contact lens, *MFN* center-near multifocal

paracentral regions of the retina, particularly with the MF lens of higher add power and MFN design.

The reduction in luminance [27] and image contrast by defocus [25],potentially can decrease the amplitude of mfERG response. [28] Therefore, appropriate optical correction during exam recording is recommended to minimize the reduction in macular response [25]. Previous studies involving ERG or mfERG analysis with optical defocus have used strategies with a single focal plane. In the current study were applied MF lens with different focal planes, competing with each other, and the amount of defocus varies from the center to the periphery according to the MF design. Despite the differences in design, the total amount of light passing through the entire of the MF lens power rings is equal in both designs, which implies that the total of luminance reduction is equivalent when comparing both MFs. The difference in the local distribution of focused light and a re-distribution of energy on the retina may explain the differences in the mfERG response observed from the center to the periphery. However, the influence of the luminance reduction induced by the MF lens cannot be fully discharged, as demonstrated by the differences in mfERGs with the SVCL lens (Experiment 1) with dilated pupil that helps control pupil size and luminance.

Two of the most relevant factors for changes in pupil diameter, are luminance (decrease with higher luminance) and accommodation (decrease with accommodation effort). During both experiments, we have maintained the same luminance and accommodation conditions (correct compensation for stimulus viewing distance with additional optical correction that varies with the MF design). Therefore, we assume that fluctuations in pupil size and accommodation were residual and should not have a major effect or alter the interpretation of the results. In experience #2, the pupil of the presbyopic subjects was not dilated in order to preserve normal physiological conditions as much as possible. However, senile miosis may be an important limiting factor to record reliable mfERG signals. Considering the impact of pupil size on the performance of multifocal optical correction, pupil dilation in these subjects, as required by ISCEV Standards, would completely alter the visual conditions that were intended to be evaluated. Interestingly, the current results show that under dilated conditions, in young subjects, no significant differences were observed in the mfERG response between the different MF designs (in Experiment #1). In contrast, in Experiment #2, presbyopic patients under non-dilated conditions showed significant changes in the mfERGs responses comparing the two MF designs. It would be relevant to understand whether these changes are design-specific and whether this information can be used to objectively follow-up the response of the

visual system to predict the patient´s ability to successfully adapt to a multifocal optical correction.

The presence of a system in the retina, which produces equal sensitivity and rapid transfer of information from increased and decreased of light and contrast [29–31], combined with the cellular origin of the mfERG response [32, 33] may help to explain the changes found with the different MFs, We found a significant increase in implicit time in both N1 and P1 peak wave components in Experiment #1 (Fig. 2A, B) with both MF designs. Furthermore, the increase is more significant in the superior temporal and nasal retina, which may suggest a different cellular configuration between these regions. However, this needs further investigation with a larger sample size and with induction of different levels of defocus and contrasts between in different regions and cell origins**.**

In patients wearing contact lenses for presbyopia correction has been reported a delayed cortical response, measured with visual evoked potentials (VEP), [10, 15, 16]. Degradation of the retinal images such as those caused by image blur and reduced luminance, reduces mfERG more strongly than VEPs [34–37]. The present preliminary results (experiment #2) show that MFN affects the mfERG response more significantly and this effect tends to decrease after 15 days of MFN wear. Despite the changes in amplitude, with the MFN lens the implicit time N1 and P1 showed a significant increase on day 1 that does not persist 15 days after MF wear (Fig. 4 and Fig. 5). These results suggest that there may be an adaptive process in the short-to-medium term after MFs wear that begins at the retinal level. Current results should be interpreted as evidence that this delay in time may be the underlying cause of the reported cortical delays. Whether this phenomenon is due to biological changes in the retina or to changes in image quality by the MF warrants further investigation including measurement of VEPs to verify if the delay in cortical response is also observed 15 days after MF wear**.**

A limitation of experiment#1 and #2 is that it reports only the result to one eye, whereas vision is a binocular task and multifocal correction benefit from the effects of binocular summation. [6, 21]. In addition, the small sample size in experiment #2 and the fact that no mydriatic agents were used in this subsample are potential limitations. Therefore, the effects observed in experiment#2, which are based on an observation of only four cases, should be taken with caution as they can only serve to generate hypothesis that need to be confirmed in further experiments. The results should be understood in the context of a hypothesis-driven study, so that a quantitative analysis of the response time at the retinal level may be relevant to understand the neural adaptation to challenges caused by multifocal solutions in presbyopia correction**.** In addition, the results of experiment #2 show that, even without pupil dilation,it is possible to obtain consistent mfERG values from the whole retina, which makes it possible to work under physiological conditions and therefore to evaluate the visual system in a clinical condition.

In summary, from these preliminary evaluations, a reduction in amplitude and delay in time of the mfERG wave response is observed when a different level of defocus are induced by different MF designs. This may suggest a change in retinal pathway activity in response to contrast changes due to multifocality and the adaptive process perceived in MF wearers, may begin at the retinal level. To the best of our knowledge, these are the first results in this field and provide the background for future studies.

Funding This study was founded by Portuguese Foundation for Science and Technology (FCT, PTDC/FIS-OPT/0677/2014); FCT Strategic Funding (UID/FIS/04650/2013) and FCT-SFRH/BPD/92365/2013 (to Paulo Fernandes) and FCT-SFRH/BD/136684/2018 (to Ana Amorim-de Sousa).

Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial in the subject matter or materials discussed in this manuscript.

Ethical approval The study was approved by the Ethics Subcommittee for Life and Health Sciences (SECVS) of the University of Minho.

Informed consent Informed consent was obtained from all individual participants included in the study.

Statement of human rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the Code of Ethical Conduct of the University of Minho and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statement on the welfare of animals Not applicable.

References

1. Bennett ES (2008) Contact lens correction of presbyopia. Clin Exp Optom 91(3):265–278. https://doi.org/10.1111/j.1444-0938.2007.00242.x
2. Marsack J, Thibos L, Applegate R (2004) Metrics of optical quality derived from wave aberrations predict visual performance. J Vis 4(4):322–328. https://doi.org/10.1167/4.4.8
3. Vinas M, Benedi-Garcia C, Aissati S, Pascual D, Akondi V, Dorronsoro C, Marcos S (2019) Visual simulators replicate vision with multifocal lenses. Sci Rep 9(1):1539. https://doi.org/10.1038/s41598-019-38673-w
4. Piers P, Fernandez E, Manzanera S, Norrby S, Artal P (2004) Adaptive optics simulation of intraocular lenses with modified spherical aberration. Invest Ophthalmol Vis Sci 45(12):4601–4610. https://doi.org/10.1167/iovs.04-0234
5. Fernandes P, Neves H, Lopes-Ferreira D, Jorge J, González-Meijome J (2013) Adaptation to multifocal and monovision contact lens correction. Optom Vis Sci 90(3):228–235. https://doi.org/10.1097/OPX.0b013e318282951b
6. Escandón-García S, Ribeiro FJ, McAlinden C, Queirós A, González-Méijome JM (2018) Through-focus vision performance and light disturbances of 3 new intraocular lenses for presbyopia correction. J Ophthalmol 31(2018):6165493. https://doi.org/10.1155/2018/6165493
7. Rosa A, Miranda A, Patrício M, McAlinden C, Silva F, Castelo-Branco M, Murta J (2017) Functional magnetic resonance imaging to assess neuroadaptation to multifocal intraocular lenses. J Cataract Refract Surg 43(10):1287–1296. https://doi.org/10.1016/j.jcrs.2017.07.031
8. Rosa AM, Miranda ÂC, Patrício M, McAlinden C, Silva F, Murta N, Castelo-Branco M (2017) Functional magnetic resonance imaging to assess the neurobehavioral impact of dysphotopsia with multifocal intraocular lenses. Ophthalmology 124(9):1280–1289. https://doi.org/10.1016/j.ophtha.2017.03.033
9. Ho W, Wong O, Chan YC, Wong SW, Kee CS, Chan HH (2012) Sign-dependent changes in retinal electrical activity with positive and negative defocus in the human eye. Vision Res 52(1):47–53. https://doi.org/10.1016/j.visres.2011.10.017
10. Zeri F, Berchicci M, Naroo SA, Pitzalis S, Di Russo F (2018) Immediate cortical adaptation in visual and non-visual areas functions induced by monovision. J Physiol 596(2):253–266. https://doi.org/10.1113/JP274896
11. Shimizu K, Ito M (2011) Dissatisfaction after bilateral multifocal intraocular lens implantation: an electrophysiology study. J Refract Surg 27(4):309–312. https://doi.org/10.3928/1081597X-20100804-01
12. Rosén R, Lundström L, Unsbo P (2012) Sign-dependent sensitivity to peripheral defocus for myopes due to aberrations. Invest Ophthalmol Vis Sci 53(11):7176–7182. https://doi.org/10.1167/iovs.11-9034
13. Khanal S, Turnbull PRK, Lee N, Phillips JR (2019) The effect of atropine on human global flash mfERG responses to retinal defocus. Invest Ophthalmol Vis Sci 60(1):218–225. https://doi.org/10.1167/iovs.18-24600
14. González-Méijome JM, Peixoto-de-Matos SC, Faria-Ribeiro M, Lopes-Ferreira DP, Jorge J, Legerton J, Queiros A (2016) Strategies to regulate myopia progression with contact lenses. Eye Contact Lens 42(1):24–34. https://doi.org/10.1097/ICL.0000000000000100
15. Imbeau L, Majzoub S, Thillay A, Bonnet-Brilhault F, Pisella PJ, Batty M (2017) Presbyopia compensation: looking for cortical predictors. Br J Ophthalmol 101(2):223–226. https://doi.org/10.1136/bjophthalmol-2015-307581
16. El Ameen A, Majzoub S, Pisella P-J (2017) Recherche d'indices électrophysiologiques de confort visuel après correction de la presbytie par lentilles de contact. J Fr Ophtalmol 40(4):257–263. https://doi.org/10.1016/j.jfo.2016.10.014
17. Zhang X (2003) Simultaneously recording local luminance responses, spatial and temporal interactions in the visual system with m-sequences. Vision Res 43(15):1689–1698. https://doi.org/10.1016/s0042-6989(03)00040-3
18. Chen JC, Brown B, Schmid KL (2006) Changes in implicit time of the multifocal electroretinogram response following contrast adaptation. Curr Eye Res 31(6):549–556. https://doi.org/10.1080/02713680600744869
19. Plainis S, Ntzilepis G, Atchison DA, Charman WN (2013) Through-focus performance with multifocal contact lenses: effect of binocularity, pupil diameter and inherent ocular aberrations. Ophthalmic Physiol Opt 33(1):42–50. https://doi.org/10.1111/opo.12004
20. Faria-Ribeiro M, González-Méijome JM (2019) Multifocal contact lenses: towards customisation? Ophthalmic Physiol Opt 39(1):37–45. https://doi.org/10.1111/opo.12597
21. Fernandes P, Amorim-de-Sousa A, Queirós A, Escandón-Garcia S, McAlinden C, González-Méijome JM (2018) Light disturbance with multifocal contact lens and monovision for presbyopia. Cont Lens Anterior Eye 41(4):393–399. https://doi.org/10.1016/j.clae.2018.03.006
22. Amorim-de-Sousa A, Moreira L, Macedo-de-Araújo R, Amorim A, Jorge J, Fernandes PR, Queirós A, González-Méijome JM (2020) Impact of contact lens materials on the mfERG response of the human retina. Doc Ophthalmol 140(2):103–113. https://doi.org/10.1007/s10633-019-09722-6
23. Hoffmann MB, Bach M, Kondo M, Li S, Walker S, Holopigian K, Viswanathan S, Robson AG (2021) ISCEV standard for clinical multifocal electroretinography (mfERG) (2021 update). Doc Ophthalmol 142(1):5–16. https://doi.org/10.1007/s10633-020-09812-w.6
24. Lopes-Ferreira D, Neves H, Queiros A, Faria-Ribeiro M, Peixoto-de-Matos SC, González-Méijome JM (2013) Ocular dominance and visual function testing. Biomed Res Int 2013:238943. https://doi.org/10.1155/2013/238943
25. Chan H, Siu AW (2003) Effect of optical defocus on multifocal ERG responses. Clin Exp Optom 86(5):317–322. https://doi.org/10.1111/j.1444-0938.2003.tb03127.x
26. Chin MP, Chu PH, Cheong AM, Chan HH (2015) Human electroretinal responses to grating patterns and defocus changes by global flash multifocal electroretinogram.

PLoS ONE 10(4):e0123480. https://doi.org/10.1371/journal.pone.0123480
27. Schimitzek T, Bach M (2006) The influence of luminance on the multifocal ERG. Doc Ophthalmol 113(3):187–192. https://doi.org/10.1007/s10633-006-9028-7
28. Gonzalez P, Parks S, Dolan F, Keating D (2004) The effects of pupil size on the multifocal electroretinogram. Doc Ophthalmol 109(1):67–72. https://doi.org/10.1007/s10633-004-1545-7
29. Euler T, Haverkamp S, Schubert T, Baden T (2014) Retinal bipolar cells: elementary building blocks of vision. Nat Rev Neurosci 15(8):507–519. https://doi.org/10.1038/nrn3783
30. Schiller PH, Sandell JH, Maunsell JH (1986) Functions of the ON and OFF channels of the visual system. Nature 322(6082):824–825. https://doi.org/10.1038/322824a0
31. Schiller PH (2010) Parallel information processing channels created in the retina. Proc Natl Acad Sci USA 107(40):17087–17094. https://doi.org/10.1073/pnas.1011782107
32. Hood DC (2000) Assessing retinal function with the multifocal technique. Prog Retin Eye Res 19(5):607–646. https://doi.org/10.1016/s1350-9462(00)00013-6
33. Hood DC, Frishman LJ, Saszik S, Viswanathan S (2002) Retinal origins of the primate multifocal ERG: implications for the human response. Invest Ophthalmol Vis Sci 43(5):1673–1685
34. Herbik A, Hölzl GC, Reupsch J, Hoffmann MB (2013) Differential effects of optic media opacities on mfERGs and mfVEPs. Clin Neurophysiol 124(6):1225–1231. https://doi.org/10.1016/j.clinph.2012.11.020
35. Herbik A, Reupsch J, Thieme H, Hoffmann MB (2014) Differential effects of optic media opacities on simultaneous multifocal pattern electroretinograms and visual evoked potentials. Clin Neurophysiol 125(12):2418–2426. https://doi.org/10.1016/j.clinph.2014.03.017
36. Chen JY, Hood DC, Odel JG, Behrens MM (2006) The effects of retinal abnormalities on the multifocal visual evoked potential. Invest Ophthalmol Vis Sci 47(10):4378–4385. https://doi.org/10.1167/iovs.06-0242
37. Pieh C, Hoffmann MB, Bach M (2005) The influence of defocus on multifocal visual evoked potentials. Graefes Arch Clin Exp Ophthalmol 243(1):38–42. https://doi.org/10.1007/s00417-004-0969-9