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Cortical dynamics in visual areas induced by the first use of multifocal contact lenses in presbyopes

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A R T I C L E I N F O

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A B S T R A C T

A common non-spectacle strategy to correct presbyopia is to provide simultaneous images with multifocal optical designs. Understanding the neuroadaptation mechanisms behind multifocal devices usage would have important clinical implications, such as predicting whether patients will be able to tolerate multifocal optics. The aim of this study was to evaluate the brain correlates during the initial wear of multifocal contact lenses (CLs) using high-density visual evoked potential (VEP) measures. Fifteen presbyopes (mean age 51.8 ± 2.6 years) who had previously not used multifocal CLs were enrolled. VEP measures were achieved while participants looked at arrays of 0.5 logMAR Sloan letters in three different optical conditions arranged with CLs: monofocal condition with the optical power appropriate for the distance viewing; multifocal correction with medium addition; and multifocal correction with low addition. An ANOVA for repeated measures showed that the amplitude of the C1 and N1 components significantly dropped with both multifocal low and medium addition CL conditions compared to monofocal CLs. The P1 and P2 components showed opposite behavior with an increase in amplitudes for multifocal compared to monofocal conditions. VEP data indicated that multifocal presbyopia corrections produce a loss of feedforward activity in the primary visual cortex that is compensated by extra feedback activity in extrastriate areas only, in both early and late visual processing.

1. Introduction

Around 1.3 billion people worldwide are currently affected by presbyopia [1]. Although presbyopia can be easily corrected by spectacles, [2] many presbyopes do not have an adequate optical correction, resulting in a significant adverse impact on their quality of life and burden on productivity, especially in lower-income countries [3]. Contact lenses (CLs) and surgical approaches are spectacle-free options for presbyopia correction that employ a variety of different strategies, such as simultaneous images, monovision, restored accommodative dynamics, and pinhole depth of focus expansion [4]. Among these strategies, the most common is to provide simultaneous images with multifocal optical designs managed by CLs, intraocular lenses (IOLs), corneal laser ablation, or corneal inlays. Through the simultaneous-image principle, different areas of the optical zone of a multifocal lens simultaneously provide powers for far and near distance correction over the entrance pupil [2]. Since these areas are concentric and rotationally symmetrical, they induce a certain amount of spherical aberration that increases the depth of focus of the eye system, representing a "passive" approach to correcting the accommodation impairment due to presbyopia (sometimes referred to as pseudo-accommodation) [5]. The depth of focus of the spherically aberrated system is always higher than the

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equivalent non-aberrated, or diffraction-limited, system [6]. However, spherical aberration compromises the Optical Transfer Function of that optical system at the best focus (determined by Modulation Transfer Function and Phase Transfer Function) [6], causing a contrast sensitivity loss. Patient satisfaction with multifocal IOLs [7] and CLs [8] is not uniform and not fully predictable, and although the reasons for individual tolerance to these multifocal devices are unknown, it has been suggested that overcoming visual disturbances due to the drawbacks of these devices may be dependent on neural adaptation [9]. Therefore, understanding the neuroadaptation mechanisms behind multifocal optical device use would have important clinical implications, such as helping to predict whether patients will be able to tolerate multifocal optics, and it could guide a surgeons' decision about the surgical implantation of this type of optical device [7,10]. Nevertheless, so far, presbyopia and multifocal optical devices have been investigated mainly with clinical studies, which have assessed visual performances, and only very few studies have looked at neural adaptation to multifocal devices. In a recent study, Rosa et al. [11] used functional magnetic resonance imaging (fMRI) to explore brain correlates of dysphotopsia, which is a particular flaw of bilateral multifocal IOLs implantation. Dysphotopsia is reported by patients as giving them the symptom of disability or discomfort glare. The results of that study showed that the neuroadaptation process to multifocal IOLs is present three weeks after the implantation of the IOL, with increased activity of cortical areas dedicated to top-down attention and involved in effortful actions (fronto-parietal circuits), procedural learning, cognitive control (cingulate cortex), and goal-oriented behavior (caudate). Such effects were interpreted by the authors as the initial phase of neuroadaptation to multifocal IOLs. While Rosa et al. [11] demonstrated that multifocal optical devices induced cortical functional changes in high-order associative cortices, no direct effects were observed in the visual areas, thus the possible functional changes induced by multifocal contact lenses (MCLs) in visual processing remain unexplored. A potential source of information about the effect of multifocal devices on visual processing in the brain might come from the analysis of the event-related potentials (ERP) such as the visual evoked potential (VEP), which is a particularly suited method to study the visual processing dynamics along the visual pathways in the striate and extrastriate visual regions. More specifically, VEP studies have mainly focused on the modulation of well-known early components, such as the C1 originating in the striate cortex (V1) and the P1, N1, and P2 originating in extra-striate visual cortices of the occipital lobe (V3A, V4) and the posterior parietal cortex [12]. More recent VEP studies have also shown the presence of prefrontal activities such as the prefrontal N1 (pN1) and P1 (pP1) peaking at 100 and 150 ms respectively. Several studies, combining ERP and fMRI methods localized these components within the anterior insular cortex [13,14]. VEPs have previously been used by this research group to test the neural adaptation process induced by monovision [15], which is an optical correction for presbyopes that has shown a good level of effectiveness [16,17]. Specifically, in Zeri et al. [15], a high-density electrode array (64-channel) was used to analyze the VEP components described above. The first clear effect of monovision on VEP was the C1 amplitude reduction, indicating that the unilateral blurring induced by monovision reduces feed-forward activity in the primary visual area. Monovision led to increased amplitude of the P1 and pP1 components and this gain was interpreted as an attentional compensatory activity used to counteract the degraded V1 signal. This result was interpreted in relation to plastic brain adaptation in visual and non-visual areas during monocular interferences. Here, the same technique has been used again, but to provide a detailed spatio-temporal analysis of the cortical activity in visual and non-visual areas just after neophyte presbyopes are corrected with MCLs. More specifically, it was hypothesized that, if the immediate cortical response to monocular interferences in monovision and spherical aberration induced by multifocal optics triggered the same general immediate cortical response, one should observe a common response to MCLs and monovision.[15] Alternatively, due to the different nature of these optical corrections, a specific different cortical response might be ignited therefore, MCLs should display a different pattern of EEG results compared to those seen in monovision.

To this aim, two different levels of addition in MCLs were tested, to enlarge the variability of the induced spherical aberration and therefore visual outcomes to better detect a possible relationship with VEP components.

2. Method

2.1. Participants

To estimate the sample size, a priori power analysis was performed using the G*Power 3.1.9.7 software [18]. The analysis was set for a 2x3 repeated measures analysis of variance (ANOVA) with within factors only and using the Cohen's f effect size. The f was based on the minimum significant power (partial eta squared) detected in the previous study on monovision,[15] which was 0.102. This value corresponded to $f = 0.337$. The alpha error probability was set to 0.05 and the power (1-β error probability) to 0.95. These parameters yielded to a sample size of 14. Participants were enrolled according to the following inclusion criteria:

- Age 45–55 years.
- Not previously fitted with MCLs.
- Absence of any known ocular pathologies, and not being subjected to ocular drug treatment or systemic drugs with known ocular effects.
- Refractive error in the range −8.00 D and + 4.00 D, with astigmatism up to 0.75 DC and an anisometropia lower than 2.00 D between the two eyes.
- Near addition required at 40 cm between + 1.00 and + 1.75 D. This narrow range allowed us to be very close to the addition level of the two CLs (low and medium) chosen for the experiment (see the CLs description in the materials and preliminary MCLs assessment section).
- Monocular best-corrected visual acuity (BCVA) at distance equal to or greater than 0.10 logarithm of the minimum angle of resolution (logMAR) (20/25) in both eyes with a difference between the two eyes lower than 0.1 logMAR.
- Having good binocular vision (no strabismus) and no anomalies with ocular motility.
- Able and willing to adhere to the study instructions and complete all specified evaluation.
- Read, indicate understanding of, and sign informed consent.

Fifteen presbyopic participants (mean age 51.8 ± 2.6 years; range 45.3–55.4 years; six males). No payment was made to the participants. All participants gave written informed consent, and all procedures were conformed to the Declaration of Helsinki and approved by the Ethics Committee of Fondazione Santa Lucia (Rome, Italy) Prot. CE/PROG.798.

2.2. Materials

The CLs used throughout the study were the silicone hydrogel daily disposable Dailies TOTAL1^{TM} (Alcon Laboratories, Fort Worth, TX, USA), which are available in both multifocal and monofocal design, made in delefilcon A material, with a back optic zone radius of 8.5 mm, the total diameter of 14.1 mm, the core equilibrium water content of 33 % and Dk/t of 156 Fatt units (at −3.00 D). For each participant, the far distance power of the MCLs was determined; the spherical equivalent refraction (SER) worked out on the monocular subjective refraction least minus/most plus was corrected for the vertex distance, and a + 0.25 D was added to it, as specified by the fitting guide of the manufacturer. For the MCL, only two additions (low and medium) were selected. According to the manufacturer, "*low addition*" allows covering patients up to + 1.25 D of minimum addition needed whereas "*medium addition*" CLs cover an of minimum addition needed between + 1.50 and + 2.00 D. The power of the monofocal CL used as control at far distance was equal to the Mean Spherical Equivalent worked out on the monocular subjective refraction least minus/most plus adjusted for the vertex distance, whereas at near distance the CLs power was equivalent to the Mean Spherical Equivalent worked out on the monocular subjective refraction least minus/most plus adjusted for the vertex distance to which the near addition of the patient was added.

2.3. Preliminary visual assessment

After the anamnesis, participants were required to answer the Italian version of the Near Activity Vision Questionnaire (NAVQ) [19] allowing a measure of the subjective satisfaction with the quality of vision at near without the use of any correction. A comprehensive eye examination of each participant was performed by the same experienced clinician before performing the VEP experiment. Ophthalmoscopy and slit-lamp examination were carried out to detect any ocular anomaly. A pupillography (Eye Top pupillometer; CSO, Florence, Italy) was performed to measure scotopic (at 0.4 lx) and photopic (at 50 lx) pupil diameters in both eyes. Ocular motility was examined by using an H pattern test and a light-pen. Eye sighting dominance was determined by the 'Hole-in-the-Card' test and quantified with a relative score [20]. Non-cycloplegic subjective refraction was carried out monocularly by a phoropter procedure with a final equalization via dissociated testing aiming to obtain the least minus/most plus. With the subjective refraction at distance arranged on a trial frame, visual acuity, binocular functionality, accommodation, and reading performance were assessed. Monocular and binocular visual acuities were measured, at both high and low contrast, at a far distance (5 m) in photopic condition. The visual acuities were measured with Sloan letters generated at high and low contrast with an LCD display optotype system (Vision Chart CSO, Florence, Italy). The actual contrast measured by a Chroma meter cs 100 A (Minolta. Tokyo, Japan) was (mean ± SD) 97.5 ± 0.1 % and 12 ± 1 % for high and low contrast letters respectively, with a luminance of the background on the display of 79 ± 3 cd/m^2. A row of five Sloan letters was presented, in descending logarithmic progression of 0.10 logMAR. A forced-choice procedure and a letter-by-letter (0.02 logMAR) scoring criteria were used to assess the threshold. Every single 5-letter row was randomly generated among twenty-eight different sets of balanced readability and presented in isolation [21]. To detect any binocular vision anomaly, always with the subjective refraction at distance arranged on a trial frame, dissociated phorias (either at far and near distance through an alternating cover test and prism bar), and fusional reserves (at far with prism bar) were assessed. The monocular amplitude of accommodation was measured by the Donder's push-up method using an RAF rule [22].

Finally, the reading performance was measured binocularly in photopic condition (see above) through the Italian language version of the Radner test, [23] and reading acuity and critical print size were determined. Once all the measurements with the subjective refraction at 5 m distance were carried out, the addition for near was firstly determined according to the expected age procedure [24] and then adjusted subjectively to obtain the final addition [22]. Then, visual acuity at near, stereoacuity, fixation disparity, suppression, and reading performance were measured with the subject wearing their full near refractive correction. Monocular and binocular visual acuity was measured both at high (96.1 ± 0.1 %) and low contrast (10.0 ± 0.1 %) at near (40 cm) in photopic condition using a set of printed charts specifically made for this purpose (background luminance of 69 ± 3 cd/m^2). Every single chart contained a series of lines of five Sloan-font letters, reduced in size with a logarithmic progression of 0.1 logMAR according to the ETDRS setup, ranging between 0.8 and −0.3 logMAR for high contrast chart and between 1.0 and 0.1 logMAR for low contrast chart. Every single five-letter line was chosen among the 28 different sets of five letters balanced for readability [21]. The same set of five letters was used only once in the same chart and the sequence of the set of five letters in the different charts was always different every single chart was used in random conjunction with the specific measure to carry out in the preliminary visual assessment and in the following assessment with CLs (see next paragraph) to avoid any possible learning effect. Stereoacuity and fixation disparity were measured at 40 cm with the Borish Vectographic Nearpoint card II (Stereo Optical Company, Chicago, IL USA). If fixation disparity was present, associated phoria (in prism diopters) was determined. The level of central suppression was measured by the modified Borish test [25] on a scale from 0 to 5 (0 = no reported suppression; 5 = constant monocular suppression of one eye). Reading performance with near correction was measured binocularly at 40 cm with the Radner test [23].

2.4. Preliminary MCLs assessment

Immediately after the preliminary visual assessment, monofocal and MCLs were fitted in a randomized order. Ten minutes after the insertion of the first lens, a slit lamp assessment was performed to judge that a proper CL centration and coverage of the cornea were achieved: CLs had to move freely at the push test and then return to their properly centered position when released. After this first check a series of measurements was carried out for each pair of lenses: high and low contrast visual acuity at far distance (monocular and binocular), high and low contrast BCVA at near (monocular and binocular), stereoacuity, central suppression, and reading performance. All these measurements were carried out following the procedures and utilizing the instruments described in the preliminary visual assessment section.

2.5. Visual variables data analysis

The Kolmogorov-Smirnov test was used to check if the results were followed a normal distribution for the visual performance variables collected in the preliminary visual assessment and in the preliminary MCLs assessment. To evaluate the differences among visual performance variables under three different conditions at far and at near distances (i.e., monofocal correction; MCLs with low; and medium addition power), the appropriate parametric statistics (paired *t*-test), or non-parametric statistics (Wilcoxon signed-rank test) were applied. For all analyses, the alpha level was fixed at 0.05. The statistical analysis was performed using SPSS, version 22 (IBM Corp., Armonk, NY, USA).

2.6. VEP experiment

2.6.1. Stimuli and procedure

The experiment was conducted in a dimly lit and quiet room. Visual stimuli were generated by Presentation® software (Version 22.1, Neurobehavioral Systems, Inc., Berkeley, CA, USA) and were presented on a linearized 21-inches CRT monitor (Philips 201B, resolution 1200 x 1600 pixels, refresh rate: 120 Hz). A string of black and white high contrast (94.0 ± 0.7 %) letter array was employed. The characters were composed of 0.5 logMAR Sloan letters, randomly arranged in a rectangular array of 176 letters distributed onto 11 rows [15]. Each rectangular matrix subtended a visual angle of 4.3 x 5.9 degrees at both examination distances (see below). The letter dimensions were chosen because they have been used in a previous VEP study in which robust VEP components [15] were evoked. A fixation dot (diameter 0.1 degrees) was constantly presented at the center of the screen. The visual stimuli were presented foveally for 250 ms on a uniform white background with an inter-stimulus interval ranging from 1 to 2 s. Stimuli were presented at two viewing distances (0.4 and 4 m) with letter dimensions that were proportionated to keep the spatial frequency constant (the letter height was 1.9 ± 0.2 mm and 19.0 ± 0.2 mm at near and far distance respectively). Background luminance of the screen resulted of 23 ±1cd/m^2, and 48 ±3cd/m^2 when the stimuli were presented at 0.4 and 4 m respectively. Illuminance at cornea level was 29 ±4 lx and 16

±2 lx at 0.4 m and 4 m, respectively.

The visual stimuli delivery was always binocular. Three kinds of visual corrections, equal in both eyes, (see also the previous paragraph) were used both at far and near distances, for a total of six correction conditions, which were randomized across participants, as follows:

1) Monofocal at far distance, arranged with monofocal CLs.
2) Multifocal “low addition” at far distance arranged with low addition MCLs.
3) Multifocal “medium addition” at far distance arranged with medium addition MCLs.
4) Monofocal at near distance arranged with monofocal CLs.
5) Multifocal “low addition” at near distance arranged with low addition MCLs.
6) Multifocal “medium addition” at near distance arranged with medium addition MCLs.

The experimental sessions consisted of five 90 s runs for each experimental condition to deliver a total of 300 stimuli for each condition. Pauses were allowed between runs, bringing the session duration to about one hour. During the recording session, participants were instructed to maintain stable fixation on the central dot, which flashed every 4–9 s, and participants having to count the flashes in each run to keep high attention on the stimulus. The CLs were inserted 10 min before starting the electroencephalographic (EEG) recording of each condition, to reach a good comfort level, and to avoid the presence of reflex tearing and an excessive blink rate.

2.7. Electrophysiological recording and data analysis

The EEG was recorded using three 32-channel BrainAmp™ amplifiers (BrainProducts GmbH., Munich, Germany) using 64 active non-polarizable sintered Ag/AgCl scalp sensors (ActiCap™) mounted according to the 10–10 International System, which were initially referenced to the left mastoid (M1) and then re-referenced to M1 + M2. In addition, horizontal eye movements were monitored from electrodes at the left and right outer canthi using a bipolar recording. Blinks and vertical eye movements were recorded with an electrode below and one above the left eye using a bipolar recording. The EEG recording was digitized at 250 Hz with an amplifier band-pass (0.01–100 Hz) including a 50 Hz notch filter and was stored for off-line averaging [15]. Fig. 1 shows the used 10–10 electrodes montage from a top-flat view.

Offline analysis was performed utilizing the BrainVision™ Analyzer 2.2 software (BrainProducts GmbH., Munich, Germany). The EEG signal was separately segmented for each condition into 400 ms epochs (from 50 ms before to 350 ms after stimulus onset). Raw EEG was filtered (0.1–25 Hz, zero phase shift Butterworth filter) and then eye movements’ artifacts were processed using the independent component analysis (ICA) algorithm [26]. Trials with amplitude exceeding the threshold of ± 70 μV were automatically excluded from the averaging. To select the intervals and electrodes to be considered in statistical analysis, the “collapsed localizer” method was used,[27] in which a localizer ERP is obtained by collapsing (averaging) all experimental conditions. To identify the interval of analysis, from the collapsed localized was calculated the global field power (GFP). The GFP describes the ERP spatial variability at each time point considering all scalp electrodes simultaneously resulting in a reference-independent descriptor of the potential field. The 0–350 ms VEP interval in which the GPF peaks were larger than 80 % of its maximum value was used for further analysis.[28] This analysis selected six foci of activity in frontal and parieto-occipital areas corresponding to the main VEP components in the following four intervals: C1 = 72–96 ms, P1 and pN1 = 84–112 ms, N1 and pP1 = 120–140 ms, P2 = 220–272 ms. To select the electrodes to be considered in statistical analysis, those with amplitude larger than 80 % of the maximum value in the selected intervals were jointed in spatial pools. Three foci of activity were clearly present, the frontal activity of the pN1 and pP1, the medial parieto-occipital activity of the C1, and the bilateral parieto-occipital of the P1, N1, and P2 components. The pN1 and the pP1 were then represented by a frontal pool containing 13 electrodes (Fp1, Fpz, Fp2, AF7, AF3, AFz, AF4, AF8, F3, F1, Fz, F2, F4). The C1 was represented by a medial parieto-occipital pool containing 6 electrodes (CPz, P1, Pz, P2, POz, Oz). The P1, N1, and P2 were represented by a bilateral parieto-occipital pool containing 12 electrodes (P7, P3, PO9, PO7, PO3, O1, O2, PO4, PO8, PO10, P4, P8).

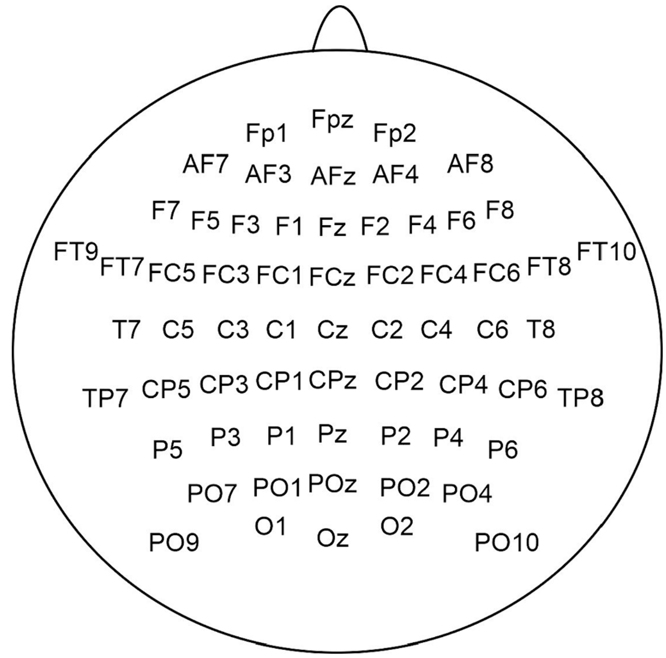

Fig. 1. 10–10 electrode montage and names used in the study. Top-flat view.

To test VEP reliability, the inter-subject variability was evaluated using the inter-subject coefficient of variation (CoV = SD/mean) for each studied component amplitude. The CoV was 15.9 %, 18.3 %, 15.0 %, and 14.1 % for the C1, P1, N1 and P2 components, respectively. These values were quite similar, and lower than 20 %, indicating a good inter-subject reliability [29,30] of the present VEP measures.

Data were then analyzed using a 3 x 2 repeated measure analysis of variance (ANOVA) separately for each component. In each analysis, the first factor was the Correction (monofocal vs. multifocal low addition vs. multifocal medium addition) and the other factor was the Viewing Distance (near vs. far). Post-hoc comparisons were executed using the Bonferroni correction to reduce the likelihood of type 1 errors from multiple comparisons. Further, individual amplitudes of each component (both at a far and near distance with the three different corrections; monofocal, multifocal low addition, and multifocal medium addition) were correlated with binocular visual acuity measured both at high and low contrast for each correction using Pearson’s or Spearman’s correlations depending on the normality of distribution of the variables considered. For all analyses, the alpha level was fixed at 0.05. To visualize the voltage topography of the VEP components, spherical spline interpolated top-flat views 120° wide were constructed using BrainVision Analyzer 2.2.[15].

3. Results

3.1. Visual assessment

The SER of monocular subjective refraction least minus/most plus at far distance was −0.72 ± 2.01 D (range 1.00 to −6.38 D) and

−0.87 ± 2.03 D (range 1.00 to −6.50 D) for right and left eye, respectively with a required addition for near in both eye of 1.50 ± 0.09 D (range 1.25 to 1.75 D). The amplitude of accommodation was 2.29 ± 0.35 D (range 1.85 to 2.94 D) in the right eye and 2.34 ± 0.41 D (range 1.85 to 3.13 D) in the left one. The NAVQ score resulted of 63 ± 14 (range 33 to 85). These results show a typical functional profile of a mid-presbyopic condition: low amplitude of accommodation, a significant level of addition required at near, and poor subjective satisfaction for near vision at NAVQ, demonstrated by a Rasch score higher than cut off for symptomatic presbyopes [19,31]. Visual outcomes of participants are reported analytically in Table 1 (visual acuities, stereopsis, fixation disparity) and Table 2 (reading performance). These results offer an overview of the visual performance at far and near distances achieved with MCLs in comparison with monofocal CLs and spectacles correction. MCLs allowed to achieve a good level of high contrast visual acuity both at far distance (Binocular level of −0.10 logMAR ± 0.06 for low addition MCLs and −0.04 logMAR ± 0.08 for medium addition MCLs) and at near distance (Binocular level of 0.03 logMAR ± 0.08 for low addition MCLs and −0.03 logMAR ± 0.05 for medium addition MCLs). However, monocular, and binocular high contrast and low contrast BCVA both at far and near distances achieved with low and medium MCLs resulted significantly lower than monofocal correction for the specific distance tested provided by spectacles (paired *t*-test; $p < 0.001$). The performance of the two different CLs, monocular and binocular BCVA at high contrast resulted significantly different both at distance and near (paired *t* test; $p < 0.01$) whereas no differences were found for low contrast BCVA. Associated phoria and central suppression did not result significantly different between near correction with spectacles and MCLs both for low and medium addition, and also between the two MCLs (Wilcoxon-Signed Rank test). Stereopsis resulted significantly better with near correction with spectacles than MCLs both for low and medium addition (p-values 0.014 and 0.020 respectively), but no differences were found between the two CLs. However, this reduction in stereopsis induced by both MCLs is clinically lower compared to the reduction induced by monovision correction.[15] Concerning the reading performance, as expected, both monofocal correction at near distance and the two kinds of MCLs significantly improved reading acuity measured by the Radner test compared to the simple correction at far distance (Wilcoxon test; $p = 0.001$, $p = 0.002$ and $p = 0.001$ for monofocal correction at near distance with spectacles, low-and medium addition MCLs, respectively). Also, for the critical print size (CPS) the same results were achieved (Wilcoxon-Signed Rank test; $p = 0.001$). Monofocal correction for near distance with spectacles provided better reading acuity and CPS than low addition MCLs ($p = 0.002$ and $p = 0.004$, respectively) but only better reading acuity compared to medium addition MCLs ($p = 0.02$) whereas no difference was found for CPS ($p = 0.11$). Both reading acuity and CPS resulted better with medium addition MCLs than low addition MCLs ($p < 0.002$).

Table 2
Mean ± SD (range) of reading acuity and critical print size (CPS) measured with the Radner test in four conditions: with optical correction at far distance (maximum impairment due to presbyopia), with optical correction at near distance, and with the two kinds of MCLs used in the experiment: low and medium addition. The logarithm of the minimum angle of resolution (logMAR).

	Correction at far distance	Correction at near distance	Low addition MCLs	Medium addition MCLs
Reading Acuity (logMAR)	0.28 ± 0.09 (0.20/0.43)	−0.01 ± 0.09 (-0.10/0.10)	0.14 ± 0.06 (0.00/-0.21)	0.06 ± 0.06 (-0.10/0.14)
CPS (logMAR)	0.45 ± 0.09 (0.30/0.60)	0.16 ± 0.08 (0.00/0.30)	0.29 ± 0.08 (0.20/0.40)	0.21 ± 0.06 (0.10/0.30)

3.2. VEP data

Fig. 2 shows the VEP waveforms at the selected pools (also graphically specified in insets) for the three corrections overlapped at the two viewing distances. The earliest visible VEP component is the C1 with onset at 60 ms and peak at 85–95 ms on medial centroparietal sites. The P1, the N1, and the P2 peaked at 100, 140, and 240–250 ms, respectively, over bilateral parieto-occipital sites. The prefrontal N1 and P1 (the pN1 and the pP1) peaked at 105 and 130 ms, on frontal and prefrontal sites. Scalp topography of all the studied VEP components is reported in Fig. 3 showing their typical topographical distribution focusing on parieto-occipital and frontal areas. In the first interval (72–112 ms), the C1, the P1, and the pN1 were visible. The C1 showed a radial negative distribution over the medial parieto-occipital site. The P1 showed a bilateral parieto-occipital distribution. The pN1 showed a medial frontopolar focus. In the second interval (124–152 ms), the N1 had focal distribution over lateral parieto-occipital areas and the pP1 was visible with a frontal distribution. The P2 (200–272 ms) had a bilateral parietal-occipital distribution similar to that of the P1.

Results of statistical analysis are reported in Table 3, while the mean amplitude (and standard errors) of the analyzed components are reported in Fig. 4. The C1 component showed a significant main effect of Correction. Bonferroni post-hoc comparisons showed larger amplitudes ($p < 0.001$) for the monofocal condition than for the multifocal low and

Table 1
Visual assessment outcomes with monofocal spectacles, monofocal CLs and MCLs. For spectacles and monofocal CLs, there were considered the outcomes with the correction for far distance when visual variables were measured at far distance (BCVA at high and low contrast at far) and the outcomes with correction for near when visual variables were measured at near (BCVA at high and low contract at near, stereoacuity, fixation disparity, and central suppression). Best-corrected visual acuity (BCVA), Right eye (RE), Left eye (LE), Binocular (B), Logarithm of the minimum angle of resolution (logMAR), Prismatic Diopters (Δ).

	Spectacles (monofocal) (Mean ± SD; min/max)	Monofocal CLs (Mean ± SD; min/max)	Low addition MCLs (Mean ± SD; min/max)	Medium addition MCLs (Mean ± SD; min/max)
High Contrast VA at far (logMAR)	RE: −0.12 ± 0.06; 0.00/-0.20 LE: −0.12 ± 0.07; −0.02/-0.24 B: −0.17 ± 0.06; −0.06/-0.26	RE: −0.10 ± 0.10; 0.10/-0.20 LE: −0.08 ± 0.10; 0.12/-0.24 B: −0.15 ± 0.09; 0.02/-0.26	RE: −0.05 ± 0.08; 0.16/-0.18 LE: −0.02 ± 0.10; 0.20/-0.14 B: −0.10 ± 0.06; 0.02/-0.18	RE: 0.04 ± 0.07; 0.16/-0.10 LE: 0.06 ± 0.10; 0.16/-0.16 B: −0.04 ± 0.08; 0.12/-0.14
Low Contrast VA at far (logMAR)	RE: 0.13 ± 0.07; 0.24/0.04 LE: 0.17 ± 0.08; 0.26/0.02 B: 0.08 ± 0.06; 0.18/-0.02	RE: 0.17 ± 0.10; 0.40/0.04 LE: 0.19 ± 0.11; 0.46/0.04 B: 0.10 ± 0.11; 0.36/-0.02	RE: 0.26 ± 0.09; 0.44/0.14 LE 0.31 ± 0.10; 0.42/0.10 B: 0.20 ± 0.09; 0.34/-0.02	RE: 0.28 ± 0.09; 0.46/0.14 LE 0.32 ± 0.11; 0.46/0.10 B: 0.24 ± 0.08; 0.36/0.08
High Contrast VA at near (logMAR)	RE: −0.06 ± 0.06; 0.06/-0.16 LE: −0.05 ± 0.07; 0.08/-0.20 B: −0.10 ± 0.07; −0.02/-0.24	RE: −0.05 ± 0.05; 0.04/-0.14 LE: −0.04 ± 0.07; 0.10/-0.18 B: −0.10 ± 0.06; −0.02/-0.22	RE: 0.11 ± 0.11; 0.30/-0.10 LE: 0.09 ± 0.13; 0.38/-0.10 B: 0.03 ± 0.08; 0.18/-0.14	RE 0.02 ± 0.07; 0.14/-0.08 LE 0.02 ± 0.07; 0.20/-0.10 B: −0.03 ± 0.05; 0.08/-0.14
Low Contrast VA at near (logMAR)	RE: 0.29 ± 0.09; 0.44/0.16 LE: 0.32 ± 0.11; 0.46/0.16 B: 0.24 ± 0.09; 0.38/0.08	RE: 0.30 ± 0.08; 0.44/0.18 LE: 0.33 ± 0.10; 0.48/0.18 B: 0.26 ± 0.08; 0.38/0.14	RE: 0.48 ± 0.15; 0.70/0.16 LE: 0.51 ± 0.16; 0.74/0.16 B: 0.45 ± 0.14; 0.62/0.08	RE 0.52 ± 0.06; 0.62/0.38 LE 0.50 ± 0.09; 0.66/0.26 B: 0.44 ± 0.08; 0.58/0.24
Stereoacuity (s of arc)	51 ± 37; 20/160	55 ± 36; 20/160	71 ± 42; 20/160	83 ± 74; 20/320
Fixation Disparity (Associated phoria, Δ)	−0.2 ± 0.5; 0.00/-2.00	−0.1 ± 0.3; 0.00/-1.00	0.0 ± 0.1; 0.0/-0.5	0.0 ± 0.1; 0.0/-0.5
Central Suppression	0.7 ± 1.4, 0/5	0.8 ± 1.3, 0/5	1.1 ± 1.5; 0/5	1.1 ± 1.6; 0/5

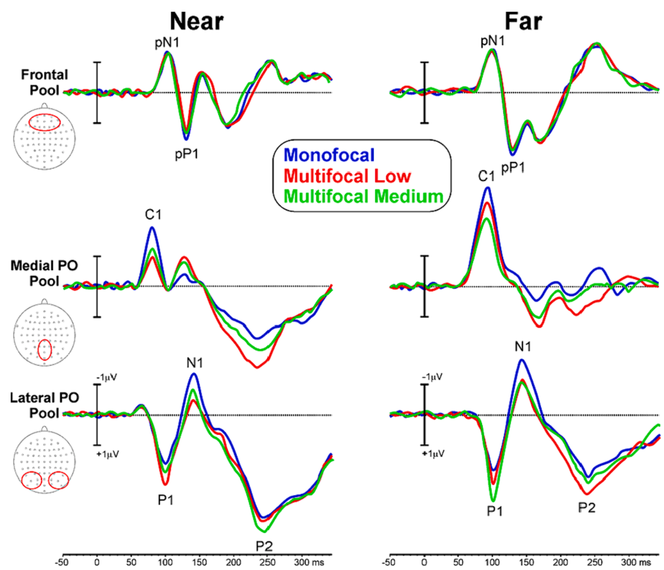

Fig. 2. Grand-averaged VEP waveforms for the three corrections (monofocal CL, low addition MCLs, and medium addition MCLs) overlapped and displayed on electrodes pools selected over frontal, medial, and bilateral parieto-occipital (PO) sites. These pools' locations are displayed in insets. On the left, VEP at near distance (0.4 m), while on the right at far distance (4 m). The considered components are labelled on the figure and time zero represents the stimulus onset.

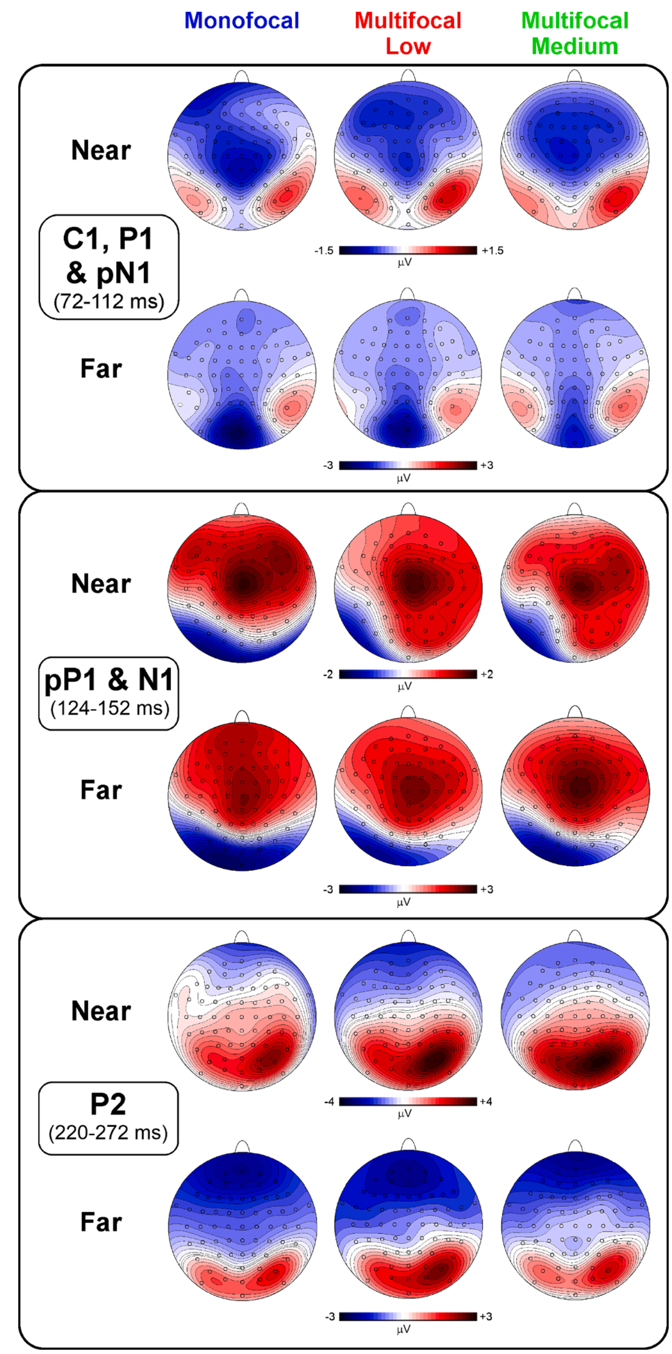

Fig. 3. Scalp topography of the grand-averaged data for the three corrections (monofocal, multifocal low addition, and multifocal medium addition) and the studied components in the relative intervals of analysis.

medium addition conditions, which did not differ from each other. The main effect of distance was also significant, with a larger amplitude for far than near distance. The interaction between correction and distance was also significant, indicating for the near distance a similar pattern of results as for the main effect of correction ($p < 0.05$), but for the far distance the monofocal condition had the largest amplitude, the multifocal medium addition condition had the smallest amplitude and the multifocal low addition condition situated in the middle. All comparisons were significant ($p < 0.01$). The P1 component showed a significant main effect of correction. Bonferroni post-hoc comparison showed smaller amplitudes ($p < 0.0001$) for the monofocal condition than for the multifocal low addition and multifocal medium addition conditions, which did not differ from each other. The main effect of distance was not significant. The interaction between correction and distance was significant, indicating for the near distance a similar pattern of results as for the main effect of correction ($p < 0.01$), but for the far distance the multifocal medium addition condition had the largest amplitude, the monofocal condition had the smallest amplitude and the multifocal low addition condition situated in the middle. All comparisons were significant ($p < 0.01$). The N1 component showed a significant main effect of Correction. Bonferroni post-hoc comparisons showed larger amplitudes ($p < 0.001$) for the monofocal condition than for the multifocal low addition and multifocal medium addition conditions, which did not differ from each other. The main effect of distance was significant, with a larger amplitude for far than near distance. The interaction between correction and distance was not significant. The P2 component showed a significant main effect of Correction. Bonferroni post-hoc comparisons showed smaller amplitudes ($p < 0.0001$) for the monofocal condition than for the multifocal low addition and multifocal medium addition conditions, which did not differ from each other. The main effect of distance was also significant, with a larger amplitude for near than far distance. The interaction between correction and distance was significant, indicating for the near distance no difference among corrections, but for the far distance, the multifocal low addition correction had a larger amplitude than the monofocal condition ($p < 0.05$). ANOVA on the pN1 and pP1 showed no significant results (all $Fs < 1$).

3.3. Correlational analyses

A series of correlational analyses between binocular visual acuities at high and low contrast achieved by participants with each of the three CLs correction conditions (monofocal, multifocal low, and medium addition) and the respective VEP amplitude of the significant components were performed and reported for the far and near distance in Figs. 5 and 6, respectively. Concerning the far distance, no significant correlation was found (Fig. 5). As far as concerned the near distance, the following outcomes were found. The C1 did not show any significant correlation with both high and low contrast visual acuity (Fig. 6a). The N1 amplitude showed a significant negative correlation with binocular visual acuity at high contrast only in the case of multifocal low addition

Table 3
ANOVA values of the main effects of correction (Corr) and distance (Dist), and of the interaction (Corr X Dist) of the components with significant effects. The partial eta squared (η_p^2) is also reported to quantify the power of the results. DoF = Degree of Freedom, Ns = Not significant.

		F	*DoF*	*P*	$\eta_p{}^2$
	Corr	32.2	2,28	<0.0001	0.697
C1	Dist	28.2	1,14	0.0001	0.668
	Corr X dist	8.9	2,28	0.0010	0.389
	Corr	37.8	2,28	<0.0001	0.727
P1	Dist	3.5	1,14	Ns	–
	Corr X dist	23.1	2,28	<0.0001	0.622
	Corr	50.8	2,28	<0.0001	0.784
N1	Dist	9.2	1,14	0.0089	0.397
	Corr X dist	1.5	2,28	Ns	–
	Corr	7.9	2,28	0.0020	0.359
P2	Dist	42.3	1,14	0.0004	0.607
	Corr X dist	5.0	2,28	0.0140	0.263

correction (r Pearson = -0.53; p < 0.05) (Fig. 6b). The P1 showed a significant correlation in the case of monofocal CLs and low addition MCLs in both cases with low contrast visual acuity (Spearman Rho = 0.61, p = 0.014, and Spearman Rho = 0.62, p = 0.014, respectively) (Fig. 6c). Finally, the P2 amplitude showed a significant correlation with binocular visual acuity at low contrast only in the case of monofocal correction (r Pearson = 0.55; p < 0.05) (Fig. 6d).

4. Discussion

It has been widely reported that multifocal IOLs and CLs can represent an effective option to enhance the visual performance and satisfaction for the presbyopic patient [4,31–33]. The general visual psychophysics outcomes achieved by the multifocal lenses used in the present study (Tables 1 and 2) confirmed the potential effectiveness of these lenses. However, visual outcomes of MCLs also showed a slight reduction of high-contrast visual acuity and a stronger reduction of low-contrast visual acuities compared to the visual acuity achieved with monofocal correction provided by spectacles or monofocal CLs. This can be explained as an effect of the reduction of the modulation transfer function of the optical system at the best focus due to the spherical aberration created by the multifocality, [6]. It has been supposed that some neuroadaptation mechanisms would act to deal with this optical limitation [9]. However, contrary to what was hypothesized in the introduction, the observed cortical response is not the same to that previously found in the condition of monovision [15]. Results clearly showed that multifocal optic induced immediate cortical changes in the visual areas in the amplitude of all the considered VEP components. The C1 component showed a significant reduction of amplitude in the case of multifocal correction with both the additions and distances. The C1 represents the afferent volley in the primary visual area V1 or Broadmann area 17 [12,34]; it is reasonable that the simultaneous images generated by multifocal could reduce the feed-forward activity of this area. Moreover, it has also been found an interaction with distance for the multifocal correction: the multifocal medium addition condition caused the strongest reduction of the C1 amplitude, more than the low addition MCLs but this is true for information at far distance. The C1 amplitude reduction might be linked to one parameter which can show the quality of the visual input in the experimental condition in which VEP components were measured: the binocular BCVA provided by the specific CLs correction. It is possible to see in Table 1 the high-contrast BCVA at far distance with medium addition MCLs, either monocular or binocular, is lower than the one achieved by low addition MCLs whereas at near distance the medium addition MCLs provided a slightly better BCVA. Thus, monofocal CLs provided better binocular visual acuity and for this condition, the C1 had the highest amplitude. However, this hypothesis is not confirmed by correlation analysis both at far (Fig. 5a) and at near distance (Fig. 6a) that did not show significant results. A possible caveat on this point is the fact that, pupil size during visual acuity and VEPs measurements was not directly measured. Therefore, it cannot be excluded that the different ambient lighting conditions between the two different settings where visual acuities and VEPs were measured might have determined different pupil sizes and therefore not the same quality of the visual input in the two conditions.

Also, the N1 component showed a significant main effect of correction. The N1 was previously localized in extrastriate visual areas and the posterior intraparietal sulcus; [12,13] it is known to be related to the encoding of visual stimuli [35] and it represents the feed-forward visual

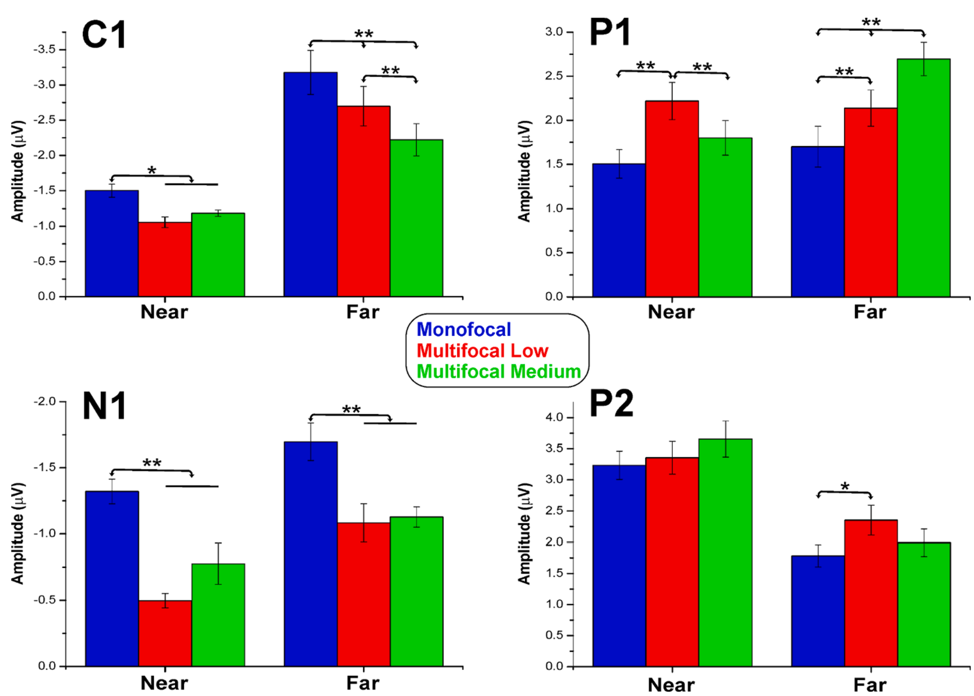

Fig. 4. Mean amplitude of the components with significant effects (*<0.05, **<0.01). Vertical bars denote standard errors.

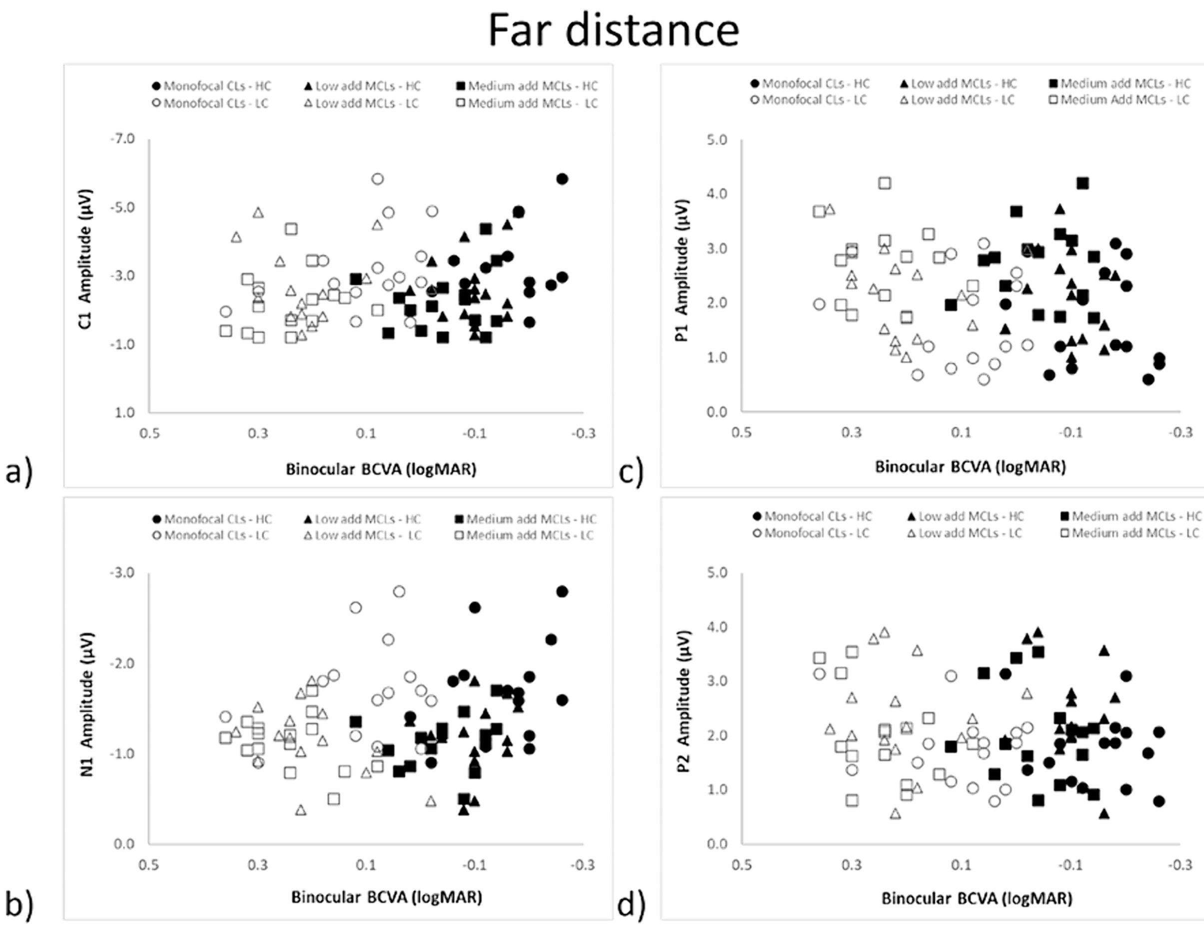

Fig. 5. Scatterplots between the binocular high contrast (HC) (black symbols) and low contrast (LC) (grey symbols) visual acuity achieved with the CLs corrections at far distance (circles, triangle and square symbols for monofocal CLs, low addition MCLs and medium addition MCLs respectively), and the amplitude of the four significant VEP components achieved during the task at far distance; C1 (a), N1 (b), P1 (c) and P2 (d). No significant correlation was found.

signal from earlier areas [12,13]. Also, in this case, one possible way to explain the reduction in N1 amplitudes at far and near distances with MCLs compared to monofocal correction is the reduction of BCVA caused by MCLs (Table 1). However, also for N1 the correlation analysis in Fig. 5b and 6b did not show that the binocular BCVA correlated to the amplitude of the N1 component both at far and near distances. In conclusion, the amplitude of the negative VEP components analyzed (C1 and N1), resulted lowered with MCLs but no clear correlation with visual acuity has been found suggesting that other aspects of visual performance linked to the simultaneous images generated by multifocal optics could play a role.

A further interesting finding of this study concerns the electrophysiological outcome observed in the multifocal conditions, such as the enhanced amplitude of the P1 and the P2 components. The P1 is sensitive to spatial attention [36,37] and it is localized in extrastriate visual areas, such as area V3A [12,37]. It is reasonable that the observed P1 effect works as an attentional compensatory activity to enhance the degraded V1 signal represented by the C1. It is interesting to note that interaction with the distance is also observed for the P1: the compensatory activity of the P1 is higher at far distances. It could be explained since in a multifocal correction the effect of the reduction of the modulation transfer function of the optical system at the best focus due to the spherical aberration created by the multifocality is more relevant at distance. However, looking at the relationship between the P1 and binocular BCVA at high and low contrast presented in Fig. 5c and 6c, only at near distance for two conditions emerged a significant correlation: the lower the BCVA the higher the amplitude. Concerning the enhancement of the P2 component for MCLs, it seems to indicate the presence of neural compensation in later visual processing, likely associated with re-entrant feedback activity from associative parietal areas to the visual cortex,[34,35] suggesting the need for additional visual compensation for multifocal correction. Once again, the correlation analysis does not provide a clear outcome that a drop in binocular BCVA represents the direct cause of the enhancement of P2 amplitude. Only the correlation between high contrast binocular BCVA and P2 amplitude at near for monofocal correction is coherent with the hypothesis (Fig. 6d).

A further result is the lack of multifocal modulation over anterior cortical areas, such as the anterior insula. This lack of non-visual effects suggests that the immediate neural compensation for multifocal correction is exclusively sensorial. It should be noted that effects in frontal brain areas were reported in an fMRI study using multifocal intraocular lenses at three weeks of correction [11]. However, the reported data were referred to different frontal areas (not insula), a different visual task (discrimination versus “passive perception”), different stimuli (gratings versus letters), different experimental designs (between groups versus cross over), optics of multifocal lenses (diffractive versus aspherical) and last, the effects disappeared after six months. Therefore, the immediate neural adaptation process induced by MCLs appears different from that observed in monovision.[15] The C1 component reduction occurred both for MCLs and monovision suggesting a similar effect of these two strategies for presbyopia correction in reducing the feed-forward activity in V1. Similarly, the P1 amplitude enhancement caused by MCLs was also observed in monovision [15], and also found by another research group [38]. Conversely, the P2 outcomes are completely different in comparison to monovision [15] in

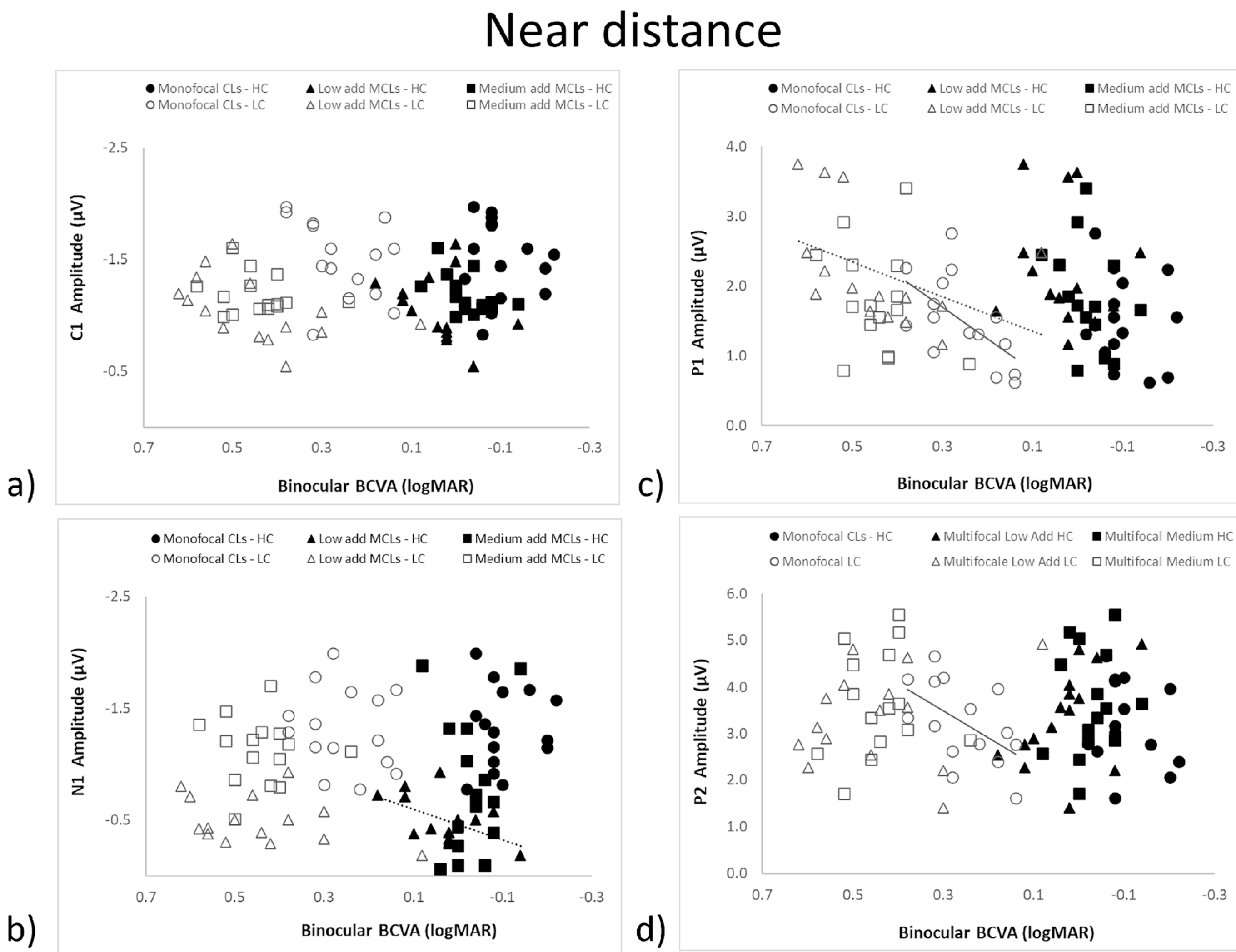

Fig. 6. Scatterplots between the binocular high contrast (HC) (black symbols) and low contrast (LC) (grey symbols) visual acuity achieved with the CLs corrections at near distance (circles, triangle and square symbols for monofocal CLs, low addition MCLs and medium addition MCLs respectively), and the amplitude of the four significant VEP components achieved during the task at near distance; C1 (a), N1 (b), P1 (c) and P2 (d). Regression lines are also reported only for significant correlation. In b) the dotted line indicates the regression between high contrast visual acuity and N1 amplitude for low addition MCLs ($r = -0.53$; $p < 0.05$). In c) the dotted line indicates the regression between low contrast visual acuity and P1 amplitude for low addition MCLs ($r = -0.61$; $p < 0.05$), whereas the solid line indicates the regression between low contrast visual acuity and P1 amplitude for monofocal CLs ($r = -0.62$; $p < 0.05$). Finally in d) the solid line indicates the regression between low contrast visual acuity and P1 amplitude for monofocal CLs ($r = -0.55$; $p < 0.05$).

which no effect was found, suggesting that no further need for additional visual compensation was necessary for monovision. On the other hand, in monovision it was clearly shown that there was a modulation within the anterior insula, and interpreted as a compensatory activity in non-visual cognitive areas [15]. This result was completely absent in MCLs suggesting that the neural compensation for multifocal correction is exclusively sensorial, while monovision is both sensorial and cognitive. However, the present study allowed achieving a snapshot only of changes in cortical responses to MCLs that did not necessarily represent correlates to the many forms of neuroadaptation that have been shown: the recovery of vision after laser refractive surgery,[39] the improvement of vision for a natural blur in uncorrected low myopes, [40,41] or in a lens-induced blur, [42], the remotion from perceptual experience of aberrations that degrade the retinal image, [43] and the improvement of visual performance through specific visual training both in uncorrected low myopic subjects [44] and in patients with phacoemulsification and multifocal IOL implantation [45]. Therefore, considering that neuroadaptation includes changes in visual performance due to many different changes in visual experience, that include different sites from the retina level [46], to the cortex,[11,47] the results of the present study cannot be extended to the overall phenomenon of neuroadaptation.

One point that should be discussed is the fact that in the present study implicit time (peak latency) differences were not found as a function of different conditions tested (monofocal vs multifocal) while in literature, peak latency differences have been also described as an effect of stimuli manipulation. The studies reporting peak latency differences, induced by blur (often only monocular) and contrast, used pattern-reversal checkerboard or gratings at 1–5 Hz and the effect was present for low spatial frequencies (from 2.3 to 4.6c/deg), medium–low contrasts (18 % to 58 %) contrast and from −8 to + 10 dioptres [48–51]. In the present study it was used a patter-onset stimulation modality with 1–2 s inter-stimulus interval, stimuli with spatial frequency of 9.6c/deg, and high contrast (94 %). As found before [52,53], with these parameters the latency effect was null, and to see latency effects the defocussing should exceed ± 3 dioptres while, in the present study, it was induced an amount of spherical aberration limited to medium addition (nominal power of maximum + 2.00 D). Although an independent characterization of the power profiles of Total 1 has not been published, the power profile of multifocal CLs by the same manufacturer limited to the first two levels of addition were lower than 3 dioptres [54]. In addition, the present pattern-onset irregular stimulus presentation is probably resistant to dioptric blur deterioration in terms of latency, likely because this stimulation modality is less sensitive to contrast changes contrary to the pattern reversal VEP [55].

This study presents further limitations. The first is that only an immediate adaptation to MCLs, in just one session, was investigated, and the changes in longer-term neuroplasticity that characterize neuroadaptation may be different. However, it should be noted that also in the previous paper on monovision, only this kind of immediate phase of adaptation was also studied, and also in neophytes [15]. This creates a more appropriate comparison between the response to these different optical strategies to correct presbyopia. A second limitation is that patients were not followed to monitor their acceptance and satisfaction with longer term wear of MCLs. Differences in the brain correlates between people fully satisfied and those not satisfied would be an interesting point to explore and open a possible understanding of the entire mechanism of adaptation. Future longer-term studies are needed to address this point.

Overall, the present VEP data indicated that, while for monovision, brain compensation of visual loss is due to larger early visual processing in extrastriate areas and also to larger sensory awareness in the insular cortex, whereas for multifocal lenses, the compensation is present only in extrastriate areas, but in both early and late visual processing. Therefore, both monovision and multifocal presbyopia corrections produce a loss of feedforward activity in the primary visual cortex that is compensated by extra feedback activity from other areas. This compensation seems to be engaged at different levels of processing of visual areas for the two kinds of corrections as a demonstration that they work using different optical strategies to which the brain responds in different ways.

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CRediT authorship contribution statement

Fabrizio Zeri: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Assunta Di Vizio:** Data curation, Writing – review & editing, Formal analysis, Investigation, Validation, Visualization. **Stefania Lucia:** Writing – review & editing, Investigation, Software. **Marika Berchicci:** Conceptualization, Data curation, Writing – review & editing, Investigation, Validation, Methodology, Software. **Valentina Bianco:** Writing – review & editing, Investigation, Software. **Sabrina Pitzalis:** Writing – original draft, Writing – review & editing, Methodology. **Silvia Tavazzi:** Funding acquisition, Writing – original draft, Writing – review & editing, Validation, Resources, Project administration. **Shehzad A. Naroo:** Conceptualization, Writing – original draft, Writing – review & editing, Methodology. **Francesco Di Russo:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Investigation, Visualization, Formal analysis, Validation, Methodology, Project administration, Resources, Software, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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