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Immediate cortical adaptation in visual and non-visual areas functions induced by monovision

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Key points

- Monovision is an optical correction for presbyopes that consists of correcting one eye for far distance and the other for near distance, creating a superimposition of an in-focus with a blurred image.
- Brain adaptation to monovision was studied in unexperienced observers by measuring visual evoked potentials from 64-channels.
- The first clear effect of monovision on visual evoked potentials was the C1 amplitude reduction, indicating that the unilateral blurring induced by monovision reduces feed-forward activity in primary visual area.
- Monovision led also to an increased amplitude of the P1 and pP1 components, with the latter originating in prefrontal regions. This effect probably works as an attentional compensatory activity used to compensate for the degraded V1 signal.

Abstract A common and often successful option to correct presbyopia with contact lenses is monovision. This is an unbalanced correction across the two eyes where one eye is corrected for far vision and the other eye is corrected for near vision. Monovision is therefore a form of acquired anisometropia that causes a superimposition of an in-focus image with a blurred image. In spite of this visual anisometropia, monovision has been successfully used for many decadesl however the brain mechanism supporting monovision is not well understood. The present study aimed to measure the visual evoked potentials with a high-density electrode array (64-channel) in a group of presbyopes and to provide a detailed spatiotemporal analysis of the cortical activity after a short period of adaptation to monovision with contact lenses. When compared with a balanced eye near correction, monovision produced both a clear reduction of the earliest visual evoked potential components, the C1 and the N1, and an amplitude increase of the P1 and pP1. These results indicate that the unilateral blurring induced by wearing monovision contact lenses reduces feed-forward activity in the primary visual area and feedback activity in extrastriate areas (C1 and N1 reduction). Interestingly, other brain activities in both extrastriate visual areas (the P1 component) and in the anterior insula (the pP1 component) appear to compensate for this dysfunction, increasing their activity during monovision. These changes confirm the presence of fluid brain adaptation in visual and non-visual areas during monocular interferences.

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Abbreviations BCVA, best corrected visual acuity; CL, contact lense; CPS, critical print size; ERP, event related potential; FBC, far balanced correction; logMAR, logarithm of the minimum angle of resolution; MSE, mean spherical

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equivalent; NAVQ, Near Activity Vision Questionnaire; NBC, near balanced correction; SSVEP, steady-state visual evoked potential; VA, visual acuity; VEP, visual evoked potential.

Introduction

Presbyopia is the physiological age-related loss in near visual function associated with a progressive reduction in accommodation and is estimated to affect 1.37 billion people worldwide by the year 2020 (Holden *et al.* 2008).

Traditionally, presbyopia has been corrected with a spectacle balanced-correction at near across the two eyes, such as reading spectacles, bifocals or progressive additional lenses (Charman, 2014). An alternative option to correct presbyopia is an unbalanced correction across the two eyes, called monovision. The simple rationale behind monovision is that one eye is corrected for far vision (usually the dominant eye), whereas the other eye is corrected for near vision. In this respect, monovision can be considered as a form of acquired anisometropia that causes a superimposition of an in-focus image with a blurred image. Despite this, monovision can be an acceptable condition for many patients because images from the blurred eye can be suppressed, with the strength of this suppression increasing with stimulus luminance and size. However, suppression is not absolute because binocular vision and stereopsis, even if impaired, still remain present. Moreover, the intraocular suppression is strongly affected by inter-individual differences (Schor *et al.* 1987). This might explain why many people adapt very quickly and effectively to monovision, whereas others tolerate this condition very badly and reject it. More recently, a relationship between personality and tolerance of blur (measured monocularly) was found (Woods *et al.* 2010), suggesting another potential source of inter-individual differences in coping with blurring. One disadvantage of the acquired anisometropia induced by monovision is the reduction of stereoacuity that drops both at far and near distance (Back *et al.* 1992). However, this reduction ranges quite widely in different studies, with high intersubject variability (Papas *et al.* 1990; Back *et al.* 1992, Harris *et al.* 1992; Kirschen *et al.* 1999; Richdale *et al.* 2006; Fernandez *et al.* 2013; Woods *et al.* 2014; Imbeau *et al.* 2016). This functional reduction could be a result of both loss of resolution and increased inhibition in the defocused eye (Simpson, 1991).

To induce monovision in presbyopic people there are two main options: contact lenses (CLs) (Bennett, 2008) and refractive surgery (Jain *et al.* 1996). According to Morgan *et al.* (2011), the worldwide percentage of monovision fittings among all the new CL fittings in presbyopic people is 36%. The level of success with monovision varies between 59% and 67% in CL wearers, and between 80% and 96% in surgery patients (Evans, 2007). Spectacles are not considered as a good option for arranging monovision because, unlike CLs and refractive surgery that are closer to the nodal point of the eye, anisometropia in spectacles will create aniseconia (i.e. a size difference in the two retinal images) and prismatic effects that are badly tolerated by subjects (Rabbetts, 2000; Evans, 2007; Kallinikos *et al.* 2012).

It is not known whether the anisometropia induced by monovision might induce some cortical functional changes in the early or late stage of the visual processing. One potentially important source of information about the effect of monovision on visual processing in the brain comes from an analysis of the visual evoked potential (VEP) that is a category of the event-related potential (ERP). The VEP reveals changes in electrocortical activity specifically associated with visual events of interest, typically characterized by modulations in amplitude and latency of components measured over a particular time period after the stimulus onset, such as early (50–250 ms) and late (300–600 ms) components, and at definite locations over the scalp. More specifically, VEP studies have mainly focused on the modulation of early components, such as the C1, the P1, the N1 and the P2, originating in striate and extra-striate visual cortices of the occipital lobe and in the posterior parietal cortex (Di Russo *et al.* 2002). However, visual stimuli evoke brain activities not only in posterior brain areas, but also at frontal sites, even though they have not consistently been labelled across studies (Makeig *et al.* 1999; Gonzalez-Rosa *et al.* 2013; Schapkin *et al.* 2014; Gajewski & Falkenstein, 2015). More recently, an increasing number of studies are showing the presence of three main prefrontal VEP activities: the earliest negative component, named prefrontal N1 (pN1), and the second positive component, named prefrontal P1 (pP1), were recorded ∼10–20 ms after the P1 and the N1 components; the last prefrontal component, named prefrontal P2 (pP2), peaked at around 350 ms after the target appearance (Berchicci *et al.* 2016). The origin of these components was localized in the anterior insula by means of recent ERP-functional magnetic resonance imaging combined recordings (Di Russo *et al.* 2016; Sulpizio *et al.* 2017). The pN1 and the pP1 were associated with an awareness of visual perception (Perri *et al.* unpublished data), whereas the pP2 has been associated with stimulus-response mapping in visual-motor tasks (Perri *et al.* 2015, 2017).

Studies on visual blurring found that monocular-induced defocus reduces foveal VEP to ∼60%, whereas defocus had no effect at eccentricities over 7° (Pieh *et al.* 2005). When defocus is induced binocularly, the amplitude of the P1 component is larger and peaks earlier than during monocular-induced defocus

(Plainis *et al.* 2011). The enhancement of VEP (larger and earlier peak amplitude of the P1 component) under binocular conditions with respect to monocular conditions is a well-known phenomenon called binocular summation effect or binocular facilitation (White & Bonelli, 1970; Harter *et al.* 1973, Amigo *et al.* 1978; Apkarian *et al.* 1981; McCulloch & Skarf, 1991) and can be useful for monitoring properties of binocular vision (Arden *et al.* 1974).

So far, there are only two studies investigating binocular VEP responses where the defocus was presented only in one eye, similarly to an induced monovision condition. Fiorentini *et al.* (1978) analysed the ERP in frequency domain (steady-state VEP; SSVEP) considering the stimulus second harmonic of SSVEP in three subjects, and found an amplitude reduction during binocular stimulation (3 cycle deg^{-1} spatial frequency). The amplitude reduction was progressively stronger when an anisometropic condition, as induced by positive lenses, was increased up to reach a plateau for a difference of +1.75 D. Berman and Seki (1982) observed that artificial anisometropia (up to +1.50 D) had no effect for spatial frequencies of 2.0 and 7.5 cycle deg^{-1} on the P1-N1 peak difference of binocular pattern-reversal VEP. Both studies used a single recording electrode at medial occipital scalp site (Oz) and a fixed (intermediate) viewing distance of 2 m.

Considering the lack of information on the cortical consequences of monovision, VEP analysis based on a high-density electrode array may help to disclose the cortical mechanisms underneath monovision adaptation, as well as identify brain markers in the visual or non-visual domain that could be predictive of success in monovision (Imbeau *et al.* 2016). The present study extends the few available notions on the electrophysiology of monovision by using whole scalp VEP in a group of presbyopes who are neophytes for monovision. Furthermore, because presbyopia mainly affects reading, letter arrays of different spatial frequencies are employed as stimuli. The present study aims to provide a detailed spatiotemporal analysis of the cortical visual activity under a monovision condition and to eventually reveal any short-term functional changes along the visual pathway induced after a short period of monovision adaptation.

Methods

Participants

Fourteen presbyopic participants (nine males; mean ± SD age: 49.5 ± 3.2 years) who had previously not been fitted with monovision CLs volunteered for the study. The inclusion criteria were the absence of any ocular pathology, monocular best corrected visual acuity (BCVA) not lower than 0.1 logarithm of the minimum angle of resolution (logMAR), with a difference between the two eyes lower than 0.1 logMAR, as well as the presence of good binocular fusion and stereopsis.

Table 1. Preliminary visual assessment outcomes

BCVA (logMAR)	RE −0.11 ± 0.06 (range 0.00/−0.20) LE −0.13 ± 0.08 (range −0.02/−0.24) *Dominant eye −0.12 ± 0.08 (range 0.00/−0.24) *Non-dominant eye −0.12 ± 0.06 (range −0.02/−0.20)
BCVA monocular difference (log MAR)	0.04 ± 0.03 (range 0.00/0.08)
Stereoacuity (sec of arc)	43 ± 43 (range 10/160)
Fixation disparity (Associated phoria) (Δ)	0.0 ± 0.7 (range 1.00/−2.00)
Central suppression	0.5 ± 1.1 (range 0/3)
Addition for near (D)	RE 1.64 ± 0.19 (range 1.25/2.00) LE 1.64 ± 0.19 (range 1.25/2.00)
Accommodation amplitude (D)	RE 2.17 ± 0.47 (range 1.54/3.33) LE 2.16 ± 0.48 (range 1.54/3.33)
NAVQ	48 ± 14 (23/71)
Mean (RE/LE) scotopic pupil diameter (mm)	5.9 ± 1.1 (7.7/3.3)
Mean (RE/LE) fotopic pupil diameter (mm)	3.7 ± 0.6 (4.5/2.7)

RE, right eye; LE, left eye; Δ, prismatic diopters; D, diopters. *BCVA data have been recalculated and reported also for the dominant and non-dominant eye to offer a comparison with the monovision condition.

All participants provided their written informed consent and all procedures conformed with the *Declaration of Helsinki* and were approved by the Ethics Committee of Fondazione Santa Lucia (Rome, Italy).

Preliminary visual assessment

A comprehensive eye and visual examination of each single participant was performed before conducting the VEP experiment. This preliminary visual examination was conducted by the same experienced clinician and was a multistepped procedure.

As a first step, an evaluation was carried out to determine whether each presbyopic volunteer was eligible in respect to the inclusion criteria described above (see results reported in Table 1). The absence of any ocular pathology was checked by direct ophthalmoscopy and slit-lamp examination. To assess whether the BCVA levels met the inclusion criteria, a procedure was initially performed aiming to determine the optical correction at far distance through a non-cycloplegic subjective refraction. This was conducted monocularly using a phoropter with a final binocular balance being performed that employed

Table 2. Mean ± SD (range) of reading acuity and CPS measured with the Radner test under three conditions: with optical correction at far distance, with optical correction at near distance and in monovision

	Correction at far distance	Correction at near distance	Monovision
Reading acuity (logMAR)	0.22 ± 0.18 (0.57/−0.08)	−0.02 ± 0.08 (0.10/−0.18)	0.08 ± 0.13 (0.30/−0.10)
CPS (logMAR)	0.44 ± 0.17 (0.70/0.20)	0.17 ± 0.12 (0.40/0.00)	0.29 ± 0.14 (0.60/0.10)

a dissociated equalization method (Borish & Benjamin, 1998). Then, BCVA was measured monocularly with the optical correction at far distance arranged in a trial frame. The measurement was performed at a distance of 5 m using high-contrast (93%) Sloan letters displayed on an LCD optotype system (Vision Chart CSO, Florence, Italy) in accordance with the Bailey–Lovie principles (Bailey & Lovie, 1976).

Finally, to assess the presence of good binocular fusion and stereopsis, a series of tests (stereoacuity, fixation disparity and central suppression) were all performed at 40 cm. For this purpose, the near addition power required for 40 cm was determined based upon an age expected procedure (Antona *et al.* 2008). The power was adjusted subjectively to obtain the final near addition (Elliott, 2003). The addition for near was added to the optical correction at far distance to obtain the optical correction at near distance for each eye.

Stereoacuity and fixation disparity were evaluated using the Borish Vectographic Nearpoint card II (Stereo Optical Company, Chicago, IL, USA) with the optical correction at near distance arranged for both eyes in a trial frame. If fixation disparity was present, then horizontal prisms were used to determine the amount of disparity, recorded in prism dioptres (associated phoria). The level of central suppression was investigated by the modified Borish test with the optical correction at near distance arranged for both eyes in a trial frame and participants were classified in accordance with the classification proposed by Zeri *et al.* (2005) on a scale from 0 (no reported suppression) to 5 (constant monocular suppression of one eye).

As a second step of the preliminary visual assessment, a series of visual and reading variables was investigated to further describe the presbyopia condition of all participants and to offer a baseline that could be used as a comparator for any reduction observed under the monovision conditions (Tables 1 and 2). Accommodative amplitude was measured with Donder's push-up method. Reading acuity and critical print size were measured binocularly using the Italian version of the Radner test (Calossi *et al.* 2014) at 40 cm with optical correction at far distance (first column in Table 2), as well as optical correction at near distance (second column in Table 2). The order of measurements with the corrections was randomized across all subjects, as well as the chart of the Radner test. To measure the impact of presbyopia in every-day life, the validated Italian version (Zeri *et al.* 2017) of the Near Activity Vision Questionnaire (NAVQ) was used. Finally, a pupillography (Eye Top pupillometer; CSO, Florence, Italy) was performed to measure scotopic (at 0.4 lux) and photopic (at 50 lux) pupil diameters in both eyes for all subjects.

In the next step of preliminary visual assessment, the power of the CLs to be used during VEP recordings was determined (Table 3). Starting with the optical correction at far distance, the mean spherical equivalent (MSE) was calculated for each eye as the algebraic sum of the value of the sphere and half of the cylindrical value. Dominance was assessed by the Hole-in-the-Card Test (Zeri *et al.* 2011). The power of CLs was determined for the three different visual corrections used in the VEP experiment according to:

(1) Far balanced correction (FBC): in both eyes, CL power was equal to the MSE, with an addition of +0.25 D to compensate for negative vergence at an examination distance of 4 m for VEP measurement (see below).
(2) Near balanced correction (NBC): in both eyes, the CL power was taken as the FBC plus an addition for near of +1.75 D.
(3) Monovision: on the dominant eye, CL power was the FBC, whereas, on the other eye, the CL power was equal to the FBC plus an addition for near of +1.75 D.

The dioptrical difference between the distance correction and the near correction was maintained at a level of +1.75 D for all participants. This was to maintain an equal level of anisometropia across participants under the monovision condition.

The final step of preliminary visual assessment was to explore the effect of monovision on visual and reading performance of the subjects (Tables 1 and 2). Each participant was fitted with CL for monovision according the power reported in Table 3, allowing familiarization with CLs to avoid any difficulty during the VEP experiment. The CL used throughout the study was the Proclear 1 day (Cooper Vision, Victor, NY, USA),

Table 3. Analytic summary of participant's optical correction at far distance, MSE and CLs used in the experiment

		Optical correction at far distance		MSE		FBC		NBC		Monovision	
Participant	Dominance	RE sph/cyl x	LE sph/cyl x	RE (D)	LE (D)	RE CL pwr (D)	LE CL pwr (D)	RE CL pwr (D)	LE CL pwr (D)	RE CL pwr (D)	LE CL pwr(D)
1	LE	0.50	0.25/0.50 × 80	0.50	0.50	0.75	0.75	2.50	2.50	2.50	0.75
2	RE	0.00	−0.5	0.00	−0.50	0.25	−0.25	2.00	1.50	0.25	1.50
3	RE	−0.75/−0.50 × 90	−0.50/−0.50 × 20	−1.00	−0.75	−0.75	−0.50	1.00	1.25	−0.75	1.25
4	LE	0.00	0.00	0.00	0.00	0.25	0.25	2.00	2.00	2.00	0.25
5	LE	−0.25 × 180	−0.25 × 180	−0.13	−0.13	0.25	0.25	2.00	2.00	2.00	0.25
6	RE	0.25	0.50	0.25	0.50	0.50	0.75	2.25	2.50	0.50	2.50
7	RE	−0.50	−0.50	−0.50	−0.50	−0.25	−0.25	1.50	1.50	−0.25	1.50
8	LE	−4.50/−0.50 × 180	−4.25/−0.50 × 180	−4.75	−4.50	−4.50	−4.25	−2.75	−2.50	−2.75	−4.25
9	LE	−0.25 × 180	–0.25 × 170	−0.13	−0.13	0.25	0.25	2.00	2.00	2.00	0.25
10	RE	1.00	1.00	1.00	1.00	1.25	1.25	3.00	3.00	1.25	3.00
11	LE	2.00/0.25 × 180	1.25/0.25 × 180	2.13	1.38	2.50	1.75	4.25	3.50	4.25	1.75
12	RE	0.25/−0.50 × 180	0.50 × 80	0.00	0.25	0.25	0.50	2.00	2.25	0.25	2.25
13	RE	0.25 × 180	0.25 × 180	0.13	0.13	0.50	0.50	2.25	2.25	0.50	2.25
14	RE	0.25	0.00	0.25	0.00	0.50	0.25	2.25	2.00	0.50	2.00

RE, right eye; LE, left eye; sph, sphere; cyl, cylinder; x, axes; pwr, Power.

Omafilcon A, back optic zone radius of 8.7 mm, total diameter of 14.2 mm and Dk/t of 28 (at −3.00 DS). Visual acuity (VA) at a distance 5 m for the eye fitted for near was measured. Stereopsis and central suppression were assessed at 40 cm. Reading acuity and critical print size (CPS) were also measured under the monovision condition (third column in Table 2) using the remaining chart from the Radner test at 40 cm.

Data analysis

The Kolmogorov–Smirnov test was used to evaluate the results for normal distribution. All of the VA measurements, as well as reading acuity and CPS, were normally distributed (all P_s = not significant); thus, a repeated measures ANOVA was performed to evaluate the differences among these variables under different cross-over conditions (i.e. optical correction at far distance, optical correction at near distance and monovision).

Stereoacuity and central suppression were not distributed normally ($P < 0.01$) and so an evaluation of their differences between the condition with optical correction at near distance and with monovision was conducted using a related samples Wilcoxon signed rank test. The statistical analysis was performed using SPSS, version 22 (IBM Corp., Armonk, NY, USA).

VEP experiment

Stimuli and procedure

The experiment was conducted in a dimly lit and quiet room. Visual stimuli were generated using Presentation, version 18.0 (Neurobehavioral Systems, Inc., Berkeley, CA, USA) and were presented on a linearized 21-inche CRT monitor (Philips 201B, Philips Electronics, Eindhoven, The Netherlands; resolution 1200 × 1600 pixels, refresh rate: 120 Hz). Two types of b/w high contrast (94%) letter array were employed; each matrix subtended a visual angle of 15 × 10°:

(i) Large 0.9 MAR Sloan letters with a maximum spatial frequency of 3.75 cycle deg^{-1}, randomly arranged to form a rectangular array of 28 letters distributed onto four rows (Fig. 1*A*).
(ii) Small 0.5 MAR Sloan letters with a maximum spatial frequency of 9.6 cycle deg^{-1}, randomly arranged in a rectangular array of 176 letters distributed onto 11 rows (Fig. 1*B*).

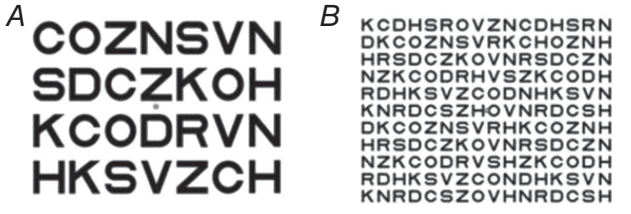

Figure 1. Stimuli used in the VEP experiment
(*A*) Large and (*B*) small letter matrix used as stimuli in the VEP experiment.

The larger letter dimensions were chosen because the corresponding spatial frequency evokes robust VEP components and they have been used in previous VEP studies (Di Russo *et al.* 2002). The smaller letters were chosen because this dimension is close to the threshold of VA in the eye with induced blur in monovision (non-dominant eye at distance and dominant eye at near). Furthermore, the defocus affects visual acuity with letters more than for gratings (Thorn & Schawartz, 1990).

A fixation dot (diameter 0.3° of visual angle) was constantly presented at the centre of the screen. The visual stimuli were presented on a uniform white background and were randomly displayed (presentation duration 250 ms) on the foveal visual field with an interstimulus interval ranging from 1 to 2 s. Stimuli were presented at two viewing distances (0.4 and 4 m), so that letter dimensions were proportionate to keep the spatial frequency constant. At 0.4 m, the large and small letters were 20 and 50 mm high, respectively. At 4 m, the large and small letters were 200 and 500 mm high, respectively. To keep ERP amplitudes sufficiently large at far distance and to make them comparable between the two distances, global monitor illuminance (brightness) was modulated to compensate for the different distances (10% at 0.4 m, 100% at 4 m).

The participants were individually tested after a 64-channel EEG active-cap was mounted on their scalp. The delivery of visual stimuli was always binocular. Three kinds of visual corrections (see above) were used into four experimental conditions randomized across participants and repeated for the two spatial frequencies, as:

(i) Far-Balanced: viewing distance 4 m. Balanced correction (FBC), ideal for far distance;
(ii) Far-Mono: viewing distance 4 m. Monovision correction: dominant eye corrected for 4 m (in-focus) and non-dominant eye corrected for near (blurred);
(iii) Near-Balanced: viewing distance 0.4 m. Balanced correction (NBC), ideal for near distance;
(iv) Near-Mono: viewing distance 0.4 m. Monovision correction: dominant eye corrected for 4 m (blurred) and non-dominant eye corrected for near (in-focus).

Hereafter, the condition of balanced binocular correction will be referred to as stereovision (either FBC or NBC), comparable to the corresponding monovision condition.

The experimental sessions consisted of five runs for each experimental condition to deliver a total of 450 stimuli

for each condition (225 trials for each spatial frequency). During the recording session, participants were instructed to maintain a stable fixation on the central dot.

The CLs were inserted to the subject ∼10 min before starting the EEG recording of each condition to ensure reaching a good comfort level and to avoid the presence of reflex tearing and an excessive blink rate.

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 in accordance with the 10-10 International System, which were referenced to the left mastoid (M1). 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.

Offline analysis was performed utilizing BrainVision Analyzer, version 2.0.1 (Brain Products GmbH). The EEG signal was separately segmented for each condition into 1200 ms epochs (from 200 ms before to 1000 ms after stimulus onset). Raw EEG data were visually inspected to identify and discard epochs contaminated with artefacts prior to the signal averaging. Eye movement artefacts were processed using the independent component analysis algorithm (Hoffmann & Falkenstein, 2008). Trials with an amplitude exceeding the threshold of ± 60 μV were semi-automatically excluded from the averaging. To further reduce high- and low-frequency noise, the group-averaged ERPs were band-pass filtered (0.1–25 Hz, zero phase shift Butterworth filter).

Peak amplitudes and latencies of the major VEP components were calculated for each subject in accordance with previous studies and scalp topography as described elsewhere (Di Russo *et al.* 2002; Di Russo & Pitzalis, 2014; Berchicci *et al.* 2016). The C1 was calculated as the maximum amplitude across Cz, CPz, Pz and POz in the 70–130 ms time window; the P1 and the P2 as the maximum amplitude between PO7 and PO8 in the 80–150 ms and 200–300 ms time windows, respectively; the N1 as the maximum amplitude across POz, Oz and Iz in the 130–170 ms time window; and the pN1 and the pP1 as the maximum amplitude over Fp1, Fp2, Fpz or AFz in the time windows 80–140 ms and 170–220 ms, respectively.

Data were analysed using a 2 × 2 × 2 repeated measures ANOVA, separately for peak amplitude and latency on the peak electrodes of each component, as: 2 (Condition: Stereovision *vs.* Monovision) × 2 (Viewing Distance: Near *vs.* Far) × 2 (Spatial Frequency: 3.75 cycle deg^{-1} *vs.* 9.6 cycle deg^{-1}). Furthermore, individual peak amplitude and the latency of each component were correlated with some optometric variables using Pearson's correlations. For all analysis, alpha level was fixed at 0.05 after Bonferroni correction for multiple comparisons.

To visualize the voltage topography of the VEP components, spherical spline interpolated top-flat views (120° wide) were constructed using BrainVision Analyzer, version 2.1.

Results

Visual assessment

A summary of preliminary visual outcomes of participants is provided in Table 1. It shows a typical functional profile of a mid-presbyopic condition: low amplitude of accommodation, significant level of addition required at near, and poor subjective satisfaction for near vision at NAVQ (demonstrated by a high Rasch score).

Monovision significantly changed some of the visual functions with respect to the condition with near distance correction: at close view, stereoacuity was impaired and the threshold passed from 43 ± 43 to 219 ± 344 s of arc ($P = 0.001$), whereas the level of central suppression increased from 0.5 ± 1.1 to 2.4 ± 2.2 ($P = 0.01$). During monovision, the VA in the non-dominant eye (being correct for near) dropped significantly for far distance, as would be expected, from -0.12 ± 0.06 (first row in Table 1) to 0.27 ± 0.08 logMAR ($t = -17.1$, $P < 0.001$). Table 2 presents the reading acuity and CPS measured with Radner test with optical correction at far distance (first column), with optical correction at near distance (second column) and in monovision (third column). ANOVA showed that both reading acuity and CPS were different across conditions ($P < 0.01$). This outcome shows that monovision is able to recover the reading performance compared to the uncorrected condition at near (i.e. with optical correction for far distance). However, there is still a certain functional gap if the monovision is compared with the full optical correction at near distance, for which reading acuity and CPS are higher.

No correlation was found between the loss of stereopsis in monovision with either photopic or scotopic pupil diameters.

VEP data

Main effects of monovision. Figure 2 shows the VEP waveforms of the stereovision and monovision conditions collapsing together the other factors (Distance and Spatial Frequency). The earliest visible VEP component is the C1 with onset at 60 ms and peak at 95 ms on CPz. The P1 and the P2 peaked at 105 and 250 ms, respectively, over bilateral PO7 and PO8 electrodes. The N1 peaked at Oz at

145 ms. The prefrontal N1 and P1 (the pN1 and the pP1) peaked at 110 and 175 ms, on AFz and Fpz, respectively. The Pp2 was not present.

Statistical analysis on the C1 showed that its latency was unaffected by monovision, whereas its amplitude was significantly reduced during monovision. By contrast, both the P1 latency and amplitude significantly increased during monovision. The N1 latency was unaffected by condition, whereas the amplitude was significantly reduced in monovision. The latency and amplitude of the P2 and the pN1 were not affected by monovision. The pP1 latency was not affected by condition, although the amplitude was significantly enhanced by monovision. Mean latencies and amplitudes are reported in Table 4, whereas statistical values are reported in Table 5.

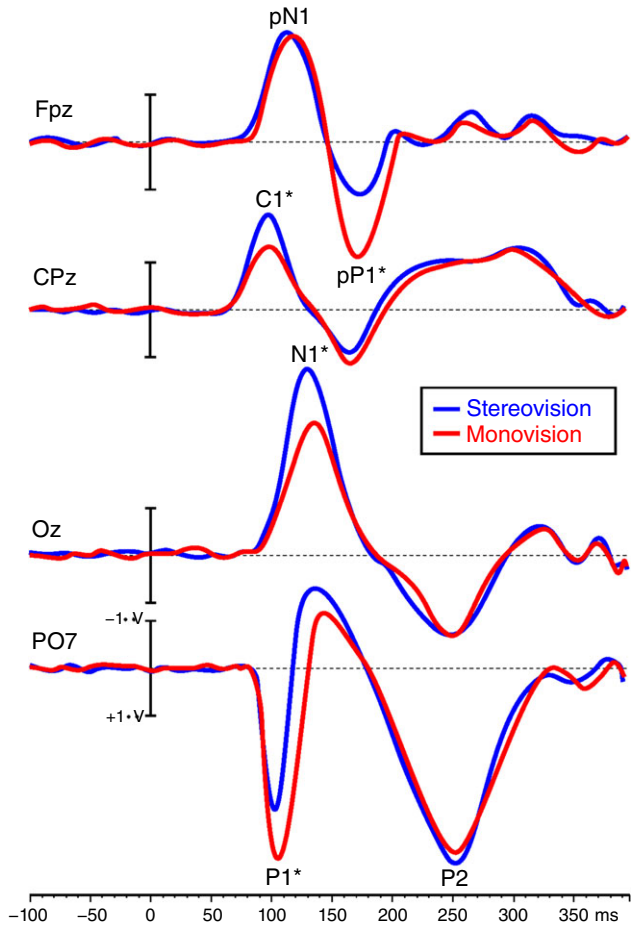

Figure 2. Grand-averaged waveforms from the VEP experiment for Stereovision and Monovision coditions
Grand-averaged waveforms of the VEP from stereovision (blue lines) and monovision (red lines) conditions displayed on the most relevant site: medial prefrontal (Fpz), medial central-parietal (CPz), medial occipital (Oz) and parietal-occipital (PO7). The other factors (i.e. distance and spatial frequency) are averaged together. The components are labelled. Time zero represents the stimulus onset and the asterisk (*) refers to the significant difference between conditions. [Colour figure can be viewed at wileyonlinelibrary.com]

Scalp topography of the main effect of monovision is shown in Fig. 3. In the first interval (70–150 ms), the C1, the P1 and the pN1 were visible. The C1 showed a radial negative distribution over medial parietal sites. The P1 showed a bilateral parieto-occipital distribution. The pN1 showed a medial frontopolar focus. In the second interval (130–170 ms), the strong N1 had focal distribution over medial-ventral occipital areas. Between 170 and 220 ms, the pP1 was visible with a bilateral prefrontal distribution. The P2 was visible in the 200–300 ms time window, with a bilateral parietal-occipital distribution similar to that of the P1.

Other effects and interactions. The viewing distance affected the latency of all of the components, being earlier in far than near probably because local brightness increasing was used to keep constant the global illumination between the two distances. The P1 and the P2 amplitude were not affected by Distance, whereas the N1 and the pP1 amplitudes were larger at far distance (Fig. 4*A*). As shown in Fig. 4*B*, Spatial Frequency affected the latency of the P1, the N1, the pN1 and the pP1, which peaked earlier for lower spatial frequency (3.75 cycle deg^{-1}). Although no effect was observed on the C1 latency, a significant three-level interaction was found on the C1 amplitude ($F_{1,13} = 17.4$, $P = 0.001$, Wilks $\lambda = 0.4$), being larger at higher (9.6 cycle deg^{-1}) than lower (3.75 cycle deg^{-1}) spatial frequency for both monovision ($P < 0.001$) and stereovision ($P = 0.004$), although at near distance only. The P1 latency showed no significant interactions, whereas the P1 amplitude had a significant Distance × Spatial Frequency interaction ($F_{1,13} = 16.6$, $P = 0.003$, Wilks $\lambda = 0.6$), indicating larger amplitude in far than near distance ($P < 0.005$), although for higher spatial frequency only. The N1, P2, pN1 and pP1 latency and amplitude showed no significant interactions.

Correlational analysis. Correlational analyses on the effect of monovision (stereovision minus monovision) were performed between VEP components (latency and amplitude) and optometric variables, collapsing together the other VEP factors (i.e. Distance and Spatial Frequency).

The reduction of the C1 amplitude in monovision positively correlated with loss in reading acuity in monovision ($r^2 = 0.30$ $P = 0.041$). The increase in both the P1 latency and amplitude in monovision correlated with the amount of VA lost for distance in the non-dominant eye (correct to close) during monovision ($r^2 = 0.29$, $P = 0.043$ for latency and $r^2 = –0.30$, $P = 0.044$ for amplitude). The increase in the pP1 amplitude correlated negatively with the amount of VA lost for distance in the non-dominant eye during monovision ($r^2 = –0.34$, $P = 0.027$) and with the reduction in reading acuity in monovision compared to stereovision ($r^2 = –0.32$, $P = 0.043$).

Table 4. Peak latencies and amplitudes of the components for each experimental condition

	Experimental condition	Latency (ms)	SD	Amplitude (μV)	SD		Latency (ms)	SD	Amplitude (μV)	SD
C1	Low SF-Near-Stereo	96	9	−2.1	2.1	**P1**	106	11	3.3	2.1
	Low SF-Near-Mono	96	8	−1.5	1.2		114	7	4.8	1.5
	Low SF-Far-Stereo	90	7	−2.6	1.8		107	14	3.6	2.2
	Low SF-Far-Mono	90	10	−1.5	0.9		112	13	4.3	2.7
	High SF-Near-Stereo	94	10	−2.3	1.3		122	11	3.2	2.7
	High SF-Near-Mono	99	10	−1.9	1.2		129	13	3.9	2.2
	High SF-Far-Stereo	92	7	−2.9	1.9		107	10	4.2	3.0
	High SF-Far-Mono	92	7	−2.2	1.1		117	7	5.5	3.3
N1	Low SF-Near-Stereo	145	13	−4.1	1.6	**P2**	225	28	4.3	2.6
	Low SF-Near-Mono	156	17	−3.2	1.8		238	32	4.4	2.4
	Low SF-Far-Stereo	137	24	−4.3	3.4		217	35	4.8	2.4
	Low SF-Far-Mono	143	21	−2.7	3.5		233	35	3.8	2.5
	High SF-Near-Stereo	172	23	−3.7	2.1		256	22	3.9	2.5
	High SF-Near-Mono	176	23	−2.2	1.8		258	27	4.7	3.7
	High SF-Far-Stereo	153	29	−3.9	3.6		230	29	4.4	2.5
	High SF-Far-Mono	154	23	−2.8	3.1		240	33	3.2	2.6
pN1	Low SF-Near-Stereo	131	25	−2.9	2.4	**pP1**	180	24	3.3	3.1
	Low SF-Near-Mono	133	29	−2.3	3.3		184	27	3.5	2.6
	Low SF-Far-Stereo	113	25	−2.4	2.8		160	24	3.4	2.0
	Low SF-Far-Mono	110	14	−2.1	3.7		157	22	3.7	2.7
	High SF-Near-Stereo	128	24	−2.2	3.0		187	25	2.9	2.5
	High SF-Near-Mono	130	27	−2.9	2.2		188	29	3.6	3.3
	High SF-Far-Stereo	118	23	−2.3	3.1		162	30	3.6	2.4
	High SF-Far-Mono	123	19	−2.4	3.2		161	23	2.9	2.0

FS, spatial frequency; Stereo, stereovision; Mono, monovision.

Discussion

The presbyopic subjects who participated in the present study were naive to monovision and so this was the first time that they experienced an anisometropic condition. The dominant eye achieved an in-focus image at far and a blur image at near, and the reverse were obtained in the non-dominant eye. We found that monovision induces short-term visual cortical changes in visual and non-visual areas, producing several changes in both the earliest and late VEP amplitude components. This is the first attempt to explore VEPs under a monovision condition compared to a balanced correction using a high-density electrode array (64-channel scalp recordings). Although Imbeau *et al.* (2016) recently used this approach to explore the electrophysiological markers that could be predictive of post-correction visual comfort in patients with presbyopia, their study reports remarkable differences compared to the present investigation. They compared monovision and multifocal CLs after 3 weeks of wearing, with at an intermediate viewing distance of 1.3 m (at this distance, the defocus rivalry has less stress effects than at near and far distances) (Charman, 2014). They showed no significant differences between the two compensation methods for either visual or VEP measures. Their study was limited to the investigation of the P1 component only. By contrast, the present study shows several clear effects of monovision on VEP waveforms starting from the C1 amplitude reduction (Fig. 2). Considering that the C1 represents the afferent volley in the visual cortex, originating in primary visual area V1 or Broadmann area 17 (Jeffreys & Axford, 1972, Di Russo *et al.* 2002), it is reasonable that the anisometric blur can reduce feed-forward activity of this area. This result agrees also with the pioneering VEP study of Fiorentini *et al.* (1978) because the SSVEP second harmonic (which they found reduced by anisometric blurring) mainly corresponds to the C1 component, as previously revealed by SSVEP-functional magnetic resonance imaging work (Di Russo *et al.* 2007). Thus, Fiorentini *et al.* (1978) found reduced V1 signals in response to a blurred vision.

Moreover, the monovision condition reduced the N1 amplitude, which was previously localized in extrastriate visual areas and in the posterior intraparietal sulcus (Di Russo *et al.* 2002, 2016). The N1 is known to be related to the encoding of visual stimuli (Hillyard *et al.* 1998) and to reflect the operation of a discrimination process within the focus of attention (Vogel & Luck, 2000). The N1 is considered to represent feed-forward visual signal from earlier areas (Di Russo *et al.* 2002, 2016); thus, the reduced

Table 5. Significant ANOVA values of main effects of monovision Condition (Cond), Distance (Dist) and Spatial frequency (SF) for latency (Lat) and amplitude (Amp) of the components

		$N_{1,13}$	P	Wilks λ			$N_{1,13}$	P	Wilks λ
C1	Cond	–	NS	–	**P1**	Cond	8.5	<0.05	0.6
Lat	Dist	12.9	<0.01	0.5	**Lat**	Dist	20.4	<0.01	0.4
	SF	–	NS	–		SF	59.5	<0.01	0.2
C1	Cond	7.7	<0.05	0.6	**P1**	Cond	5.6	<0.05	0.6
Amp	Dist	–	NS	–	**Amp**	Dist	–	NS	–
	SF	–	NS	–		SF	–	NS	–
N1	Cond	–	NS	–	**P2**	Cond	–	NS	–
Lat	Dist	8.5	<0.05	0.6	**Lat**	Dist	9.5	<0.01	0.5
	SF	25.8	<0.01	0.3		SF	–	NS	–
N1	Cond	5.9	<0.05	0.6	**P2**	Cond	–	NS	–
Amp	Dist	15.9	<0.01	0.4	**Amp**	Dist	–	NS	–
	SF	–	NS	–		SF	–	NS	–
pN1	Cond	–	NS	–	**pP1**	Cond	–	NS	–
Lat	Dist	12.0	<0.01	0.5	**Lat**	Dist	13.8	<0.01	0.4
	SF	9.4	<0.01	0.5		SF	24.1	<0.01	0.3
pN1	Cond	–	NS	–	**pP1**	Cond	4.2	0.05	0.7
Amp	Dist	–	NS	–	**Amp**	Dist	5.1	<0.05	0.7
	SF	–	NS	–		SF	–	NS	–

NS, not significant.

cortical input in V1 probably impairs the discrimination of sensory information used to facilitate stimulus encoding.

By contrast to the amplitude reduction observed in C1 and N1, monovision also determined an amplitude increase of the P1 and pP1 components, together with a delayed P1 peak latency (Fig. 2).

The available VEP literature in the field of monocular and binocular vision considers the P1 component

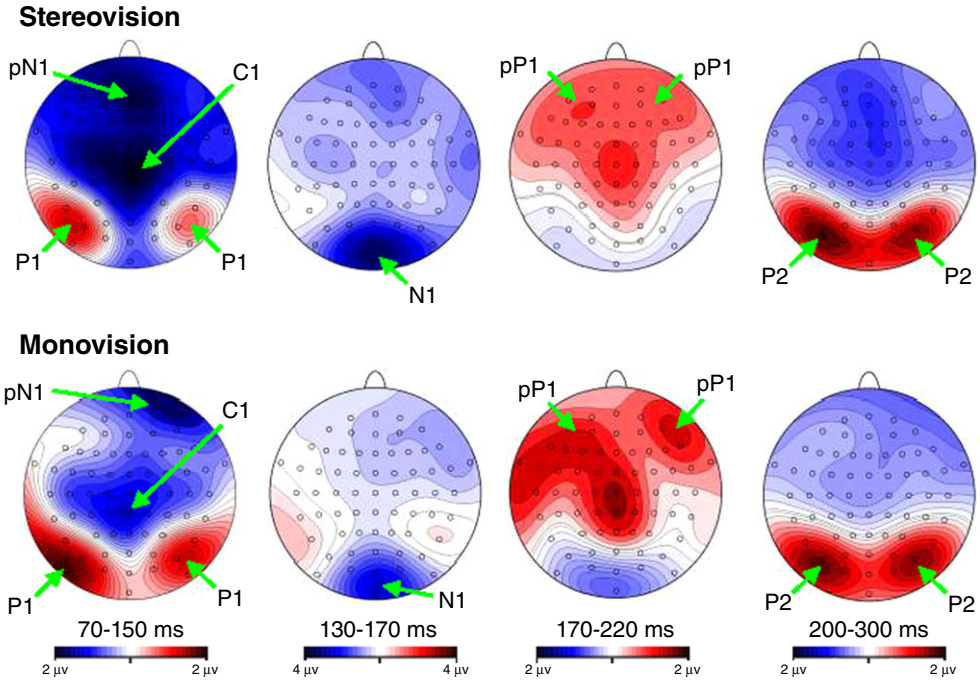

Figure 3. Topographical maps
Scalp topography of the grand-averaged data for stereovision (top) and monovision (bottom) using top-flat view maps (120°) arranged in a chronological order from left to right. The components are labelled and green arrows indicate the surface origin of the relative component. [Colour figure can be viewed at wileyonlinelibrary.com]

as a marker of binocular functionality. Generally, the P1 component in binocular condition shows a larger amplitude and a shorter latency compared to the monocular condition, and this is true also if a defocus is induced. This has been interpreted as an effected of binocular summation (White & Bonelli, 1970; Harter *et al.* 1973, Amigo *et al.* 1978; Apkarian *et al.* 1981; McCulloch & Skarf, 1991).

In the present study, VEPs were not compared during monocular and binocular conditions. The study exclusively compared binocular balanced correction (stereovision) with a still binocular view but with monocular blur (monovision or induced anisometropia). However, the monovision condition is a form of binocular impairment, as also confirmed by the significant reduction in stereopsis and central suppression observed in monovision compared to a balanced correction at near distance. If the P1 component is a marker of binocular activity, an increase in P1 latency (as found) and a reduction of the P1 amplitude should be expected, rather than an enhancement. However, no correlation between loss in stereopsis in monovision and change in the P1 amplitude between stereovision and monovision was found. Therefore, considering that the P1 is sensitive to spatial attention (Hillyard *et al.* 1973; Mangun, 1995; Luck *et al.* 2000; Di Russo *et al.* 2003) and is localized in extrastriate visual areas close to V1 such as area V3A (Di Russo *et al.* 2002, 2003, 2016), it is possible 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, in another non-spectacle form of presbyopia correction, multifocal intraocular lenses, an increased activity of cortical areas dedicated to attention (fronto-parietal circuits) was found during the

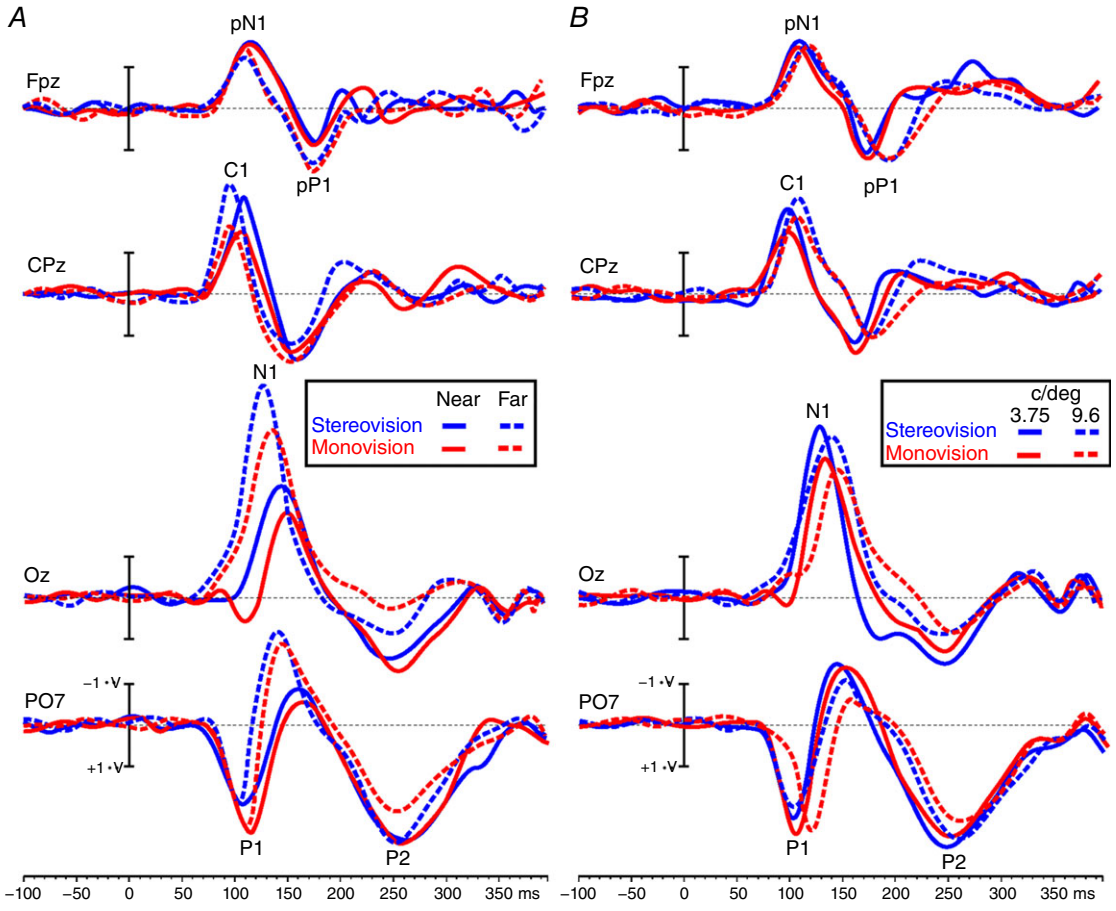

Figure 4. Grand-averaged waveforms from the VEP experiment divided for condition, viewing distance and spatial frequency
Grand-averaged waveforms of the VEP from stereovision (blue lines) and monovision (red lines) conditions reported separately for the viewing distance (*A*) and spatial frequency (*B*). For viewing distance, the continuous lines represent the near distance, whereas the dotted lines represent the far distance. For spatial frequency, the continuous lines represent the low spatial frequency (3.75 cycle deg^{-1}) and the dotted lines represent the high spatial frequency (9.6 cycle deg^{-1}). The waveforms are displayed on the most relevant site: medial prefrontal (Fpz), medial central-parietal (CPz), medial occipital (Oz) and parietal-occipital (PO7). The considered components are labelled and time zero represents stimulus onset. [Colour figure can be viewed at wileyonlinelibrary.com]

beginning of the neuroadaptation process to this type of device (Rosa *et al.* 2017).

A further interesting and unique result of the present study is the enhancement of the pP1 component by monovision. One hypothesis could be that the anterior Insula, which is the assumed cortical source of the pP1, increases its activity to further compensate for the dysfunction in V1 feed-forward activity. The interpretation of the compensation role played by the anterior Insula is supported by the positive correlation between the pP1 and VA in non-dominant eyes during monovision, as well as the reduction of reading acuity in monovision compared to stereovision. The enhancement of the pP1 appeared to be stronger at far distance where the compensation could be more useful. It has been recently proposed that the pP1 reflects the awareness of the sensory-motor integration, affecting the capacity to combine perceptual events with actions, and this is triggered by any perceptual event (Perri RL, Berchicci M, Bianco V, Quinzi F, Spinelli D & Di Russo F; unpublished data). This sensory awareness would require more effort for low-visibility stimuli, as in the case of monovision, because this requires higher gain of top-down processing on extrastriate visual areas and the anterior insula to compensate for the lower signal gain from bottom-up processing. This conclusion agrees with previous evidence indicating the insula as an area participating in 'the entry of the stimuli into awareness' (Downar *et al.* 2000). The pP1 could reflect the attention focusing occurring at early level in the perceptual processing because it emerged during passive viewing in simple and discriminative tasks. Furthermore, it is more evident in the stimulus-locked than in the response-locked ERPs, indicating a stimulus-based process (Berchicci *et al.* 2016; Perri *et al.* unpublished data). It is possible that the anterior insular activity, expressed by the pP1, might represent the non-visual, top-down control of ocular dominance allowing a stronger awareness of information coming from the in-focus eye. This hypothesis is also supported by the presence of anatomical connections between the insula and the thalamic centres (Flynn, 1999). In accordance with the neural models of Craig (2009*a*) and Damasio (2003), it can be proposed that some areas of the lateral geniculate nucleus probably project visual information to the posterior insula, and then the anterior insula processes the subjective experience of the perceptual event according to a posterior-to-anterior pattern of integration proposed for this cortex (Craig, 2009*a*,*b*). Otherwise, visual signals may reach the anterior insula from occipital areas through other connections using the dorsal pathway (Uddin *et al.* 2010).

Furthermore, it should be noted that the competition between eyes in monovision condition could be similar to binocular rivalry. It has been demonstrated that bistable perception typical of binocular rivalry is able to activate frontal-parietal cortex, even though right-lateralized (Knapen *et al.* 2011). However, frontal activity occurring in binocular rivalry is related to introspection required to evaluate rivalry rather than rivalry *per se* (Frässle *et al.* 2014).

To summarize, monovision is an efficient and functionally valid alternative binocular vision. Subjects compensate well for the unbalanced refractive error between the two eyes and are often unaware of the reduction in stereopsis and depth perception occurring during monovision, as demonstrated in the present study, as well as previous studies (Papas *et al.* 1990; Back *et al.* 1992, Harris *et al.* 1992; Kirschen *et al.* 1999; Richdale *et al.* 2006; Fernandez *et al.* 2013; Imbeau *et al.* 2016). This efficient vision is probably mediated by the peculiar type of short-term cortical changes observed in the present study. Indeed, although the amplitude was reduced in some components, such as the C1 and the N1 (originating from visual areas in striate and extrastriate cortex, as well as in the posterior intraparietal sulcus), it was even increased in some other components, such as the P1 from visual area V3a and the pP1 originating from non-visual areas such as the anterior insula.

In conclusion, the present study represents a first attempt to investigate the neurophysiological correlates of monovision, demonstrating immediate functional changes in visual and non-visual brain areas. These changes show that a unilateral blurring induced by monovision might be mediated by top-down processing in extrastriate visual areas and in the anterior insula. However, considering the adaptation phenomenon that characterizes this correction method (Wood *et al.* 2014), future studies should aim to confirm the possible association of the P1 and the pP1 with successful adaption to monovision, looking for different ERP patterns in adapted and non-adapted monovision patients.

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Additional information

Competing interests

The authors declare that they have no competing financial interests.

Author contributions

The experiments took place in the Department of Movement, Human and Health Sciences, University of Rome 'Foro Italico', Rome, Italy. All authors designed the research. FZ and MB collected the data. FZ, MB and FDR analysed the data, and all authors discussed the results and wrote the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work. All persons designated as authors qualify for authorship and all those who qualify for authorship are listed.

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