

Short-term visual cortical plasticity in visual and non-visual areas induced by monovision

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Running title:

Short-term cortical changes induced by monovision.

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Key points summary (150 words)

- Monovision is an optical correction for presbyopes that consists in 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 measuring visual evoked potentials (VEP) from 64-channels.
- 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 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 likely works as a sort of attentional compensatory activity used to compensate the degraded V1 signal.
- The results confirm the presence of brain plasticity in visual and non-visual areas during monocular interferences.

Abstract (250 words)

A common and often successful option to correct presbyopia with contact lenses (CLs) 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 decades, however the brain mechanism supporting monovision is not well understood. The aim of this study was to measure the visual evoked potentials (VEPs) with a high-density electrode array (64-channel) in a group of presbyopes and provide a detailed spatiotemporal analysis of the cortical activity after a short period of adaptation to monovision with contact lenses. When compared to a balanced eye near correction monovision produced a clear reduction of the earliest VEP components, the C1 and the N1 but conversely, the P1 and pP1 amplitude was increased. These results indicate that the unilateral blurring induced by wearing monovision CLs reduces feed-forward activity in primary visual areas and feedback activity in extrastriate area (C1 and N1 reduction). Interestingly, other brain activities in both extrastriate visual areas (the P1 component) and in the anterior insula (the pP1 component) seem to

compensate this dysfunction, increasing their activity during monovision. These changes confirm the presence of fluid brain plasticity in visual and non-visual areas during monocular interferences.

Abbreviations:

ERP, event related potential; VEP, visual evoked potential; BCVA, best corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; contact lenses, CLs.

Introduction

Presbyopia is the physiological age-related loss in near visual function associated, with a progressive reduction in accommodation, 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) whilst the other eye is corrected for near vision. In this respect, monovision can be considered a form of acquired anisometropia that causes a superimposition of an in-focus image with a blurred image. In spite of this, monovision can be an acceptable condition for many patients because images from the blurred eye can be suppressed, and the strength of this suppression increases 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 difference (Schor *et al.* 1987). This fact might explain why many people adapt very quickly and effectively to monovision, while others tolerate very badly this condition 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 difference 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 inter-subject 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 due both to 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 CLs wearers, and between 80% and 96% in surgery patients (Evans, 2007). Spectacles are not considered a good option to arrange monovision because unlike CLs

and refractive surgery that are closer to the nodal point of the eye and anisometropia in spectacles will create aniseconia (size difference in the two retinal images) and prismatic effects that are badly tolerated by subjects (Rabbetts, 2000; Evans, 2012; 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 the 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; Gajewski & Falkenstein, 2015; Gonzalez-Rosa *et al.* 2013; Schapkin *et al.* 2014). 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 approximately 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 (e.g. Berchicci *et al.* 2016). The origin of these components was localized in the anterior insula by means of recent ERP-fMRI combined recordings (Di Russo *et al.* 2016; Sulpizio *et al.* 2017). The pN1 and the pP1 were associated to the awareness of visual perception (Perri *et al.* 2017c), while the pP2 has been associated to stimulus-response mapping in visual-motor tasks (Perri *et al.* 2015, 2017a,b).

Studies on visual blurring found that monocular induced defocus reduces foveal VEP to approximately 60%, whilst defocus had no effect at eccentricities over 7 degrees (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) in 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 to monitor 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 2nd harmonic of SSVEP in three subjects, and found an amplitude reduction during binocular stimulation (3 cycle/deg spatial frequency). The amplitude reduction was progressively stronger when an anisometric condition, induced by positive lenses, was increased up to reach a plateau for a difference of +1.75D. 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 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 metres.

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, and to identify brain markers in visual or non-visual domain that could be predictive of success in monovision (Imbeau *et al.* 2015). This study will extend the few available notions on the electrophysiology of monovision, using for the latest whole scalp VEP in a group of presbyopes who are neophytes for monovision. Furthermore, since presbyopia mainly affects reading, letter arrays of different spatial frequencies are employed as stimuli. The aim of this study is to provide a detailed spatiotemporal analysis of the cortical visual activity in monovision condition and to eventually reveal any short term functional changes along the visual pathway induced after a short period of monovision adaptation.

Method

Participants

Fourteen presbyopic participants (9 males; mean age \pm SD: 49.5 \pm 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, and the presence of good binocular fusion and stereopsis.

All participants gave written informed consent and all procedures conformed to the Declaration of Helsinki and 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 performing the VEP experiment. This preliminary visual examination was conducted by the same experienced clinician and was a multi-stepped procedure.

As a first step the absence of any ocular pathology was checked by direct ophthalmoscopy and slit-lamp examination. A non-cycloplegic subjective refraction to assess if the BCVA levels met the inclusion criteria, was performed. This was conducted monocularly using a phoropter with a final binocular balance performed with 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 metres using high contrast (93%) Sloan letters displayed on an LCD optotype system (Vision Chart CSO; Florence, Italy) according to 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 40cm was determined based upon an age expected procedure (Antona *et al.* 2007). 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 according 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 second step of the preliminary visual assessment a series of visual and reading variables were investigated in order to further describe the presbyopia condition of all participants and to offer a baseline that could be used as a comparator for any reduction seen under the monovision conditions (see Tables 1 and 2). Accommodative amplitude was measured with the 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 the optical correction at far distance (Table 2, first column) and with the optical correction at near distance (Table 2, second column). The order of measurements with the corrections was randomised 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, Buckhurst et al 2012) was used. Finally, a pupillography (Eye Top pupillometer, CSO, Florence, Italy) was performed in order to measure scotopic (at 0.4 lux) and photopic (at 50 lux) pupil diameters in both eyes of all subjects.

In the next step of preliminary visual assessment the power of the CLs to be used during VEP recordings was determined (see Table 3). Starting with the optical correction at far distance the MSE was calculated for each eye as the algebraic sum of the value of the sphere and half the cylindrical value. Dominance was assessed by the *Hole-in-the-Card* Test (Zeri *et al.*, 2012). The power of contact lenses was determined according to the following:

- 1) Far balanced correction (FBC): in both eyes, CL power was equal to the MSE, with an addition of +0.25 D in order to compensate negative vergence for the 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.
- 3) Monovision: on the dominant eye CL power was the FBC, while on the other eye the CL power was equal to the FBC plus an addition for near of +1.75.

The dioptrical difference between the distance correction and the near correction was maintained at a level of +1.75D for all participants. This was to maintain an equal level of anisometropia across participants in 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 (see Tables 1 and 2). Each participant

was fitted with CL for monovision according the power reported in Table 3, allowing familiarisation 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), 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 metres for the eye fitted for near, then stereopsis, and central suppression were measured at 40 cm. Reading acuity and CPS were also measured in the monovision condition (Table 2, third column) using the remaining chart from the Radner test at 40 cm.

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)

Table 1: Preliminary visual assessment outcomes. Best corrected visual acuity (BCVA), Right eye (RE), Left eye (LE), Logarithm of minimum angle of resolution (logMAR), Prismatic Diopters (Δ), Diopters (D), Near Activity Vision Questionnaire (NAVQ).

* BCVA data have been recalculated and reported also for dominant and non-dominant eye to offer a comparison with monovision condition

	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)

Table 2: Mean ± SD (range) of reading acuity and critical print size (CPS) measured with Radner test in 3 conditions: with optical correction at far distance, with optical correction at near distance and in monovision. Logarithm of minimum angle of resolution (logMAR).

Participant	Dominance	Optical correction at far distance		MSE		FBC		NBC		Monovision	
		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	0.5	0.25/0.50x80	0.50	0.50	0.75	0.75	2.50	2.50	2.50	0.75
2	RE	0	-0.5	0	-0.5	0.25	-0.25	2.00	1.50	0.25	1.50
3	RE	-0.75/-0.50x90	-0.50/-0.50x20	-1	-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	-0.25x180	-0.25x180	-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	2.5	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/-0.50x180	-4.25/-0.50x180	-4.75	-4.50	-4.50	-4.25	-2.75	-2.5	-2.75	-4.25
9	LE	-0.25x180	-0.25x170	-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	2.00/0.25x180	1.25/0.25x180	2.13	1.38	2.50	1.75	4.25	3.5	4.25	1.75
12	RE	0.25/-0.50x180	0.50x80	0.00	0.25	0.25	0.50	2.00	2.25	0.25	2.25
13	RE	0.25x180	0.25x180	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

Table 3: Analytic summary of participant's optical correction at far distance, MSE and CLs used in the experiment. MSE (mean spherical equivalent), Far balanced correction (FBC), Near balanced correction (NBC). Right eye (RE), Left eye (LE), Sphere (sph), Cylinder (cyl), axes (x) Power (Pwr),

Data Analysis

The Kolmogorov-Smirnov test was used to evaluate the results for normal distribution. All of the VA measurements, reading acuity and CPS resulted normally distributed (all $p_s=ns$); thus, repeated measure analysis of variance (ANOVA) was performed to evaluate

the differences among these variables in 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 ($p < 0.01$), so the evaluation of their differences between the condition with optical correction at near distance and with monovision was performed by related samples Wilcoxon Signed Rank test. The statistical analysis was performed using SPSS 22 (www.ibm.com/software/analytics/spss).

VEP experiment

Stimuli and Procedure

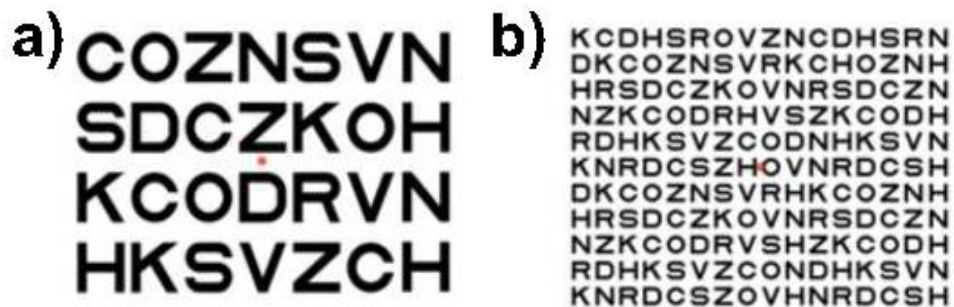
The experiment was conducted in a dimly lit and quiet room. Visual stimuli were generated by Presentation[®] software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA) and were presented on a linearized 21-inches CRT monitor (Philips 201B, resolution 1200 x 1600 pixels, refresh rate: 120 Hz). Two types of b/w high contrast (94%) letter array were employed; each matrix subtended a visual angle of 15x10 degrees:

- 1) Large 0.9 MAR Sloan letters with a maximum spatial frequency of 3.75 cycle per degree, randomly arranged to form a rectangular array of 28 letters distributed onto 4 rows (Figure 1a).
- 2) Small 0.5 MAR Sloan letters with a maximum spatial frequency of 9.6 cycle per degree, randomly arranged in a rectangular array of 176 letters distributed onto 11 rows (Figure 1b).

The larger letter dimensions were chosen, because the corresponding spatial frequency evokes robust VEP components and they have been used in previous VEP studies (e.g. 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 degrees of visual angle) was constantly presented at the center of the screen. The visual stimuli were presented on a uniform white background. The visual stimuli were randomly displayed (presentation duration 250 ms) on the foveal visual field with an inter-stimulus 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. At the two distances the monitor illuminance (brightness) was modulated to compensate the different distance (10% at 0.4 m, 100% at 4 m).



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

- 1) Far-Balanced: viewing distance 4 m. Balanced correction (FBC), ideal for far distance;
- 2) Far-Mono: viewing distance 4 m. Monovision correction: dominant eye corrected for 4 m (in-focus) and non-dominant eye corrected for near (blurred);
- 3) Near-Balanced: viewing distance 0.4 m. Balanced correction (NBC), ideal for near distance;
- 4) 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 in order 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 approximately 10 minutes before starting the EEG recording of each condition, in order to reach 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 according to 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 the BrainVision™ Analyzer 2.0.1 software (Brain Products GmbH., Munich, Germany). 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 artifacts prior to the signal averaging. Eye movements' artifacts were processed using the ICA algorithm (see Hoffmann & Falkenstein, 2008). Trials with amplitude exceeding the threshold of $\pm 60 \mu\text{V}$ 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 according to previous literature 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; 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 analyzed using a 2x2x2 repeated measure analysis of variance (RM-ANOVA) separately for peak amplitude and latency on the peak electrodes of each component, as

follows: 2 (Conditions: Stereovision vs. Monovision) x 2 (Viewing Distance: Near vs. Far) x 2 (Spatial Frequency: 3.75 c/deg vs. 9.6 c/deg). Further, individual peak amplitude and latency of each component were correlated with some optometric variables using Pearson's correlations. 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 2.1.

Results

Visual Assessment

A summary of preliminary visual outcomes of participants is reported 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 seconds of arc ($p=0.001$), whilst 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 (Table 1, first row) 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 to 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, at AFz and Fpz respectively. The Pp2 was not present.

Statistical analysis on the C1 showed that its latency was unaffected by monovision, while its amplitude was significantly reduced during monovision. On the contrary, both the P1 latency and amplitude significantly increased during monovision. The N1 latency was unaffected by condition, while 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, but the amplitude was significantly enhanced by monovision. Mean latencies and amplitudes are reported in Table 4, whereas statistical values are reported in Table 5

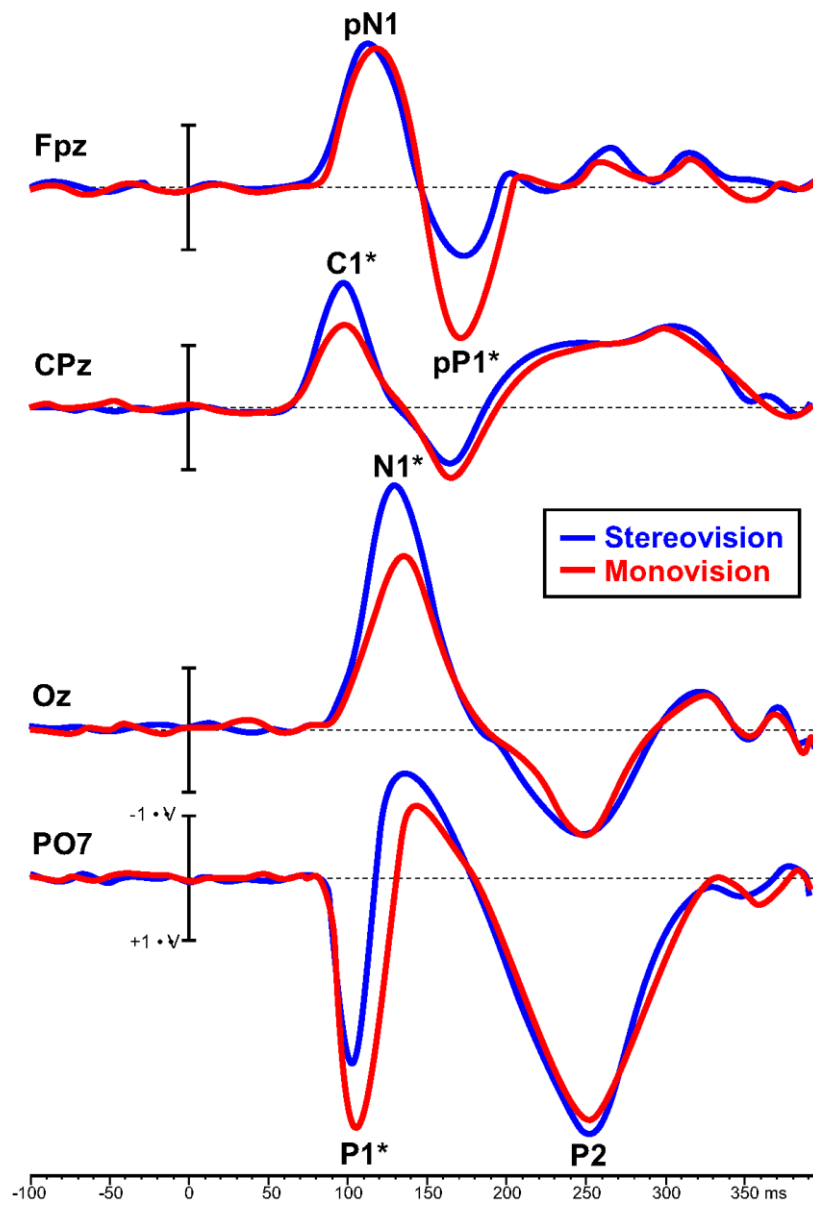


Figure 2

	Experimental condition	Lat ms	SD	Amp μV	SD		Lat ms	SD	Amp 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

Table 4. Peak latencies (Lat) and amplitudes (Amp) of the studied components for each experimental condition. Standard deviation (SD), Spatial frequency (FS), Stereo (Stereovision), Mono (Monovision).

		F(1,13)	p	Wilks λ			F(1,13)	p	Wilks λ
C1 Lat	Cond	-	<i>ns</i>	-	P1 Lat	Cond	8.5	<0.05	0.6
	Dist	12.9	<0.01	0.5		Dist	20.4	<0.01	0.4
	SF	-	<i>ns</i>	-		SF	59.5	<0.01	0.2
C1 Amp	Cond	7.7	<0.05	0.6	P1 Amp	Cond	5.6	<0.05	0.6
	Dist	-	<i>ns</i>	-		Dist	-	<i>ns</i>	-
	SF	-	<i>ns</i>	-		SF	-	<i>ns</i>	-
N1 Lat	Cond	-	<i>ns</i>	-	P2 Lat	Cond	-	<i>ns</i>	-
	Dist	8.5	<0.05	0.6		Dist	9.5	<0.01	0.5
	SF	25.8	<0.01	0.3		SF	-	<i>ns</i>	-
N1 Amp	Cond	5.9	<0.05	0.6	P2 Amp	Cond	-	<i>ns</i>	-
	Dist	15.9	<0.01	0.4		Dist	-	<i>ns</i>	-
	SF	-	<i>ns</i>	-		SF	-	<i>ns</i>	-
pN1 Lat	Cond	-	<i>ns</i>	-	pP1 Lat	Cond	-	<i>ns</i>	-
	Dist	12.0	<0.01	0.5		Dist	13.8	<0.01	0.4
	SF	9.4	<0.01	0.5		SF	24.1	<0.01	0.3
pN1 Amp	Cond	-	<i>ns</i>	-	pP1 Amp	Cond	4.2	0.05	0.7
	Dist	-	<i>ns</i>	-		Dist	5.1	<0.05	0.7
	SF	-	<i>ns</i>	-		SF	-	<i>ns</i>	-

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 studied components.

Scalp topography of the main effect of monovision is shown in Figure 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.

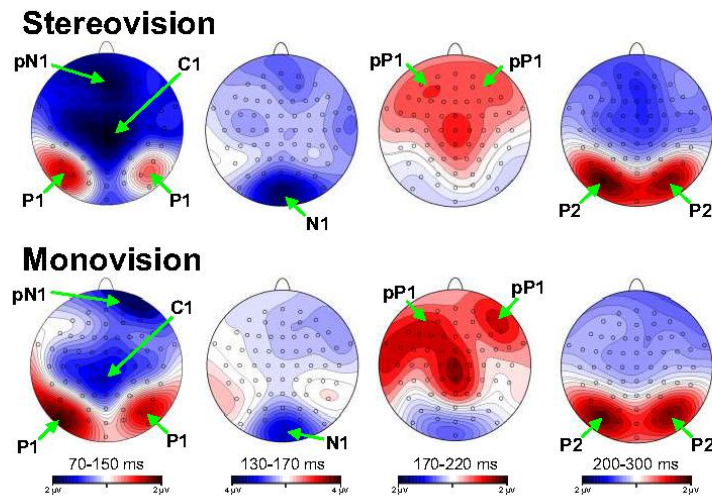


Figure 3

Other effects and interactions

The viewing distance affected the latency of all of the studied components, being earlier in far than near. The P1 and the P2 amplitude were not affected by Distance, while the N1 and the pP1 amplitudes were larger at far distance (Figure 4a). As shown in Figure 4b, the Spatial Frequency affected the latency of the P1, the N1, the pN1 and the pP1, which peaked earlier for lower spatial frequency (3.75 c/deg). Although no effect was observed on the C1 latency, a significant 3-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 c/deg) than lower (3.75 c/deg) spatial frequency for both monovision ($p<0.001$) and stereovision ($p=0.004$), but at near distance only. The P1 latency showed no significant interactions, but the P1 amplitude had a significant Distance X Spatial Frequency interaction ($F_{1,13}=16.6$, $p=0.003$, Wilks $\lambda=0.6$), indicating larger amplitude in far than near distance ($p<0.005$), but for higher spatial frequency only. The N1, P2, pN1 and pP1 latency and amplitude showed no significant interactions.

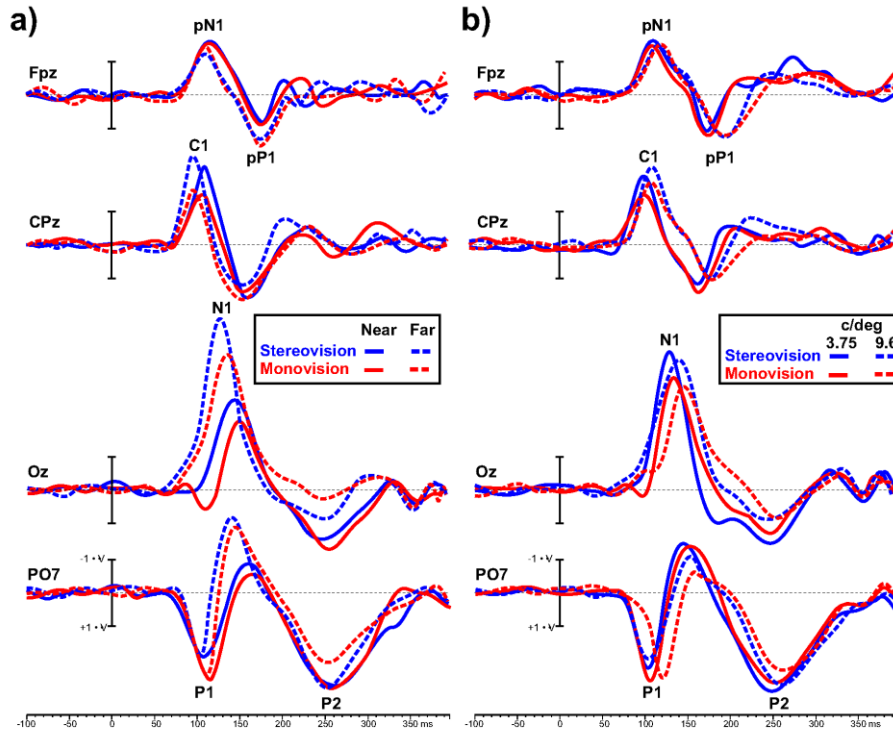


Figure 4

Correlational analyses.

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 loose in reading acuity in monovision ($r^2=0.30$ $p=0.041$). The increasing of both the P1 latency and amplitude in monovision correlated with the amount of VA lost for distance in 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 increasing of the pP1 amplitude correlated negatively with the amount of VA lost for distance in non-dominant eye during monovision ($r^2=-0.34$, $p=0.027$) and with the reduction in reading acuity in monovision compared to stereovision ($r^2=-0.32$, $p=0.043$).

Discussion

The presbyopic subjects who participated in this research were naive to monovision, so this was the first time they experienced an anisometric condition. The dominant eye

got an in-focus image at far and a blur image at near, and the reverse were obtained in the non-dominant eye.

This is the first attempt to explore VEPs in 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 presents remarkable differences with 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. In contrast, present study shows several clear effects of monovision on VEP waveforms starting from the C1 amplitude reduction (see Figure 2). Considering that the C1 represents the afferent volley in visual cortex, originating in primary visual area V1 or Brodmann area 17 (Jeffreys and 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 2nd harmonic (which they found reduced by anisometric blurring) mainly corresponds to the C1 component, as revealed by a SSVEP-fMRI work from the current study group (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), and that 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 and Luck, 2000). The N1 is supposed to represent feed-forward visual signal from earlier areas (Di Russo *et al.*, 2002; 2016), thus, the reduced cortical input in V1 likely impairs the discrimination of sensory information used to facilitate stimulus encoding.

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

Available VEP literature in the field of monocular and binocular vision considers the P1

component as a marker of binocular functionality. Generally, the P1 component in binocular condition shows a larger amplitude and a shorter latency compared to monocular condition, and this is true also if a defocus is induced. This has been interpreted as an effect 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, it is worth noting that VEPs during monocular and binocular conditions were not compared. This 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 confirmed also by the significant reduction in stereopsis and central suppression observed in monovision when compared to a balanced correction at near distance. If the P1 component is a marker of binocular activity, one should expect an increasing of P1 latency (as found) and a reduction of the P1 amplitude, 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 (e.g. Hillyard, Hink, Schwent, & Picton, 1973; Magnum, 1995; Luck *et al.* 2000; Di Russo *et al.*, 2003) and is localized in extrastriate visual areas close to V1 as area V3A (Di Russo *et al.* 2002, 2003, 2016), it is possible that the observed P1 effect works as a sort of attentional compensatory activity used to enhance the degraded V1 signal represented by the C1.

A further interesting and new 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 supposed cortical source of the pP1, increases its activity to further compensate 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 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 it is triggered by any perceptual event (Perri *et al.* 2017c). This sensory awareness would require more effort for low-visibility stimuli, as in case of monovision, because this requires higher gain of top-down processing on extrastriate visual areas and 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, since 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, pointing towards a stimulus-based process (Berchicci *et al.* 2016; Perri *et al.* 2017c). It is possible that the anterior Insular activity, expressed by the pP1, might represent the non-visual top-down control of ocular dominance allowing stronger awareness for the information coming from the in-focus eye. This hypothesis is also supported by the presence of anatomical connections between the insula and the thalamic centers (e.g. Flynn, 1999). In accordance with the neural models of Craig (2009a) and Damasio (2003), it can be proposed that some areas of the lateral geniculate nucleus likely projects 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, 2009a,b). Otherwise, visual signals may reach the anterior insula from occipital areas through other connections using the dorsal pathway (Uddin *et al.* 2010).

Taken together the present results indicate that monovision can induce short-term cortical plasticity in visual and non-visual areas. A growing body of evidence has demonstrated a residual plastic potential of adult visual cortex even though experience-dependent plasticity is reduced after the closure of the critical period (Blakemore *et al.* 1978; Issa *et al.* 1999; Sawtell *et al.* 2003; Pham *et al.* 2004; Tagawa *et al.* 2005). In humans, recent studies show that manipulating visual experience, even for short periods of time, profoundly alters the visual perception of adults (Kwon *et al.* 2009; Klink *et al.* 2010; Lunghi *et al.* 2011, 2013, 2015; Bao & Engel, 2012; Zhou *et al.* 2013a,b). In particular, Lunghi and coworkers used first psychophysical (Lunghi *et al.* 2011) and then electrophysiological (Lunghi *et al.* 2015) measurements to report that short-term monocular deprivation alters the neural activity in the adult human visual cortex at the earliest stages of visual processing (i.e., reduced C1 amplitude). Here a different form of short-term cortical adaptation was found: monovision is an efficient and functionally valid alternative binocular vision. Subjects compensate well to the unbalanced refractive error between the two eyes and are often not aware of the reduction in stereopsis and depth perception occurring during monovision as demonstrated in the present and past studies (Back *et al.* 1992, 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 likely mediated by the peculiar type of short-term cortical plasticity observed here. Indeed, while the amplitude was reduced in some components, as the C1 and the N1 (originating from visual areas in striate and extrastriate cortex, and 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 as the anterior insula. There are opposite signs of visual adaptation that should be considered evidence comparable to short-term cortical plasticity in visual and non-visual areas induced by monovision. While the functional plasticity observed in some visual areas is more in line with previous observations on monocular deprivation (i.e., lower amplitude pointing to a visual functioning reduction), the functional changes observed in the more anterior frontal areas remind to the available evidence on the neural hyper-functioning (prefrontal hyperactivity) typically observed in old people (Berchicci *et al.* 2012) or brain-damaged patients (Di Russo *et al.* 2013), who show slow but still accurate performance (i.e., greater amplitude pointing to a strategic and compensatory neural functioning). Likely, the hypo-functioning of V1 does not negatively affect the visual perception thanks to the contribution of other visual and non-visual areas, which increase their activity to compensate a reduced sensorial input, still ensuring an effective vision. In conclusion, this is a first attempt to look at the neurophysiological correlates of monovision, showing immediate functional changes in visual and non-visual brain areas. These changes confirm the presence of fluid brain plasticity during monocular interferences (Lunghi *et al.* 2015) and extend this notion showing that change in ocular dominance might be mediated by top-down processing in extrastriate visual areas and in anterior insula. However, considering the adaptation phenomenon that characterizes this correction method (Wood *et al.* 2014), future studies may verify the possible association of the P1 and the pP1 with successful adaptation to monovision, looking for different ERP patterns in adapted and non-adapted monovision patients.

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Conflicts of Interest Disclosure

The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.

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Figure captions

Figure 1: a) Large and b) Small letter matrix used as stimuli in the VEP experiment.

Figure 2: 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 considered components are labelled on the figure. Time zero represents the stimulus onset and the asterisk (*) refers to the significant difference between conditions.

Figure 3: Scalp topography of the grand-averaged data for stereovision (top row) and monovision (bottom row) using top-flat view maps (120°) arranged in a chronological order from left to right. The components are labelled on the figure and the green arrows point to the surface origin of the relative component.

Figure 4: 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 solid lines represent the near distance, whereas the dotted lines represent the far distance. For spatial frequency, the solid lines represent the low spatial frequency (3.75 c/deg) and the dotted lines represent the high spatial frequency (9.6 c/deg). 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 on the figure and the time zero represents the stimulus onset.