The Effect of Simultaneous Dual-Focus Integration on the Global Flash Multifocal Electroretinogram in the Human Eye

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Abstract

Purpose

To investigate the effect of simultaneous dual-focus (DF) on retinal activities measured by global flash multifocal electroretinogram (mfERG).

Methods

Thirty adults were recruited for mfERG measurement under three conditions: in-focus (i.e. no defocus), +2.50 D DF, and +7.50 D DF, administered using single vision contact lenses and DF lenses. The direct component (DC) and the induced component (IC) of mfERG were pooled into central macular (0°–8°), para-macular (8°–18°), and peri-macular (18°–30°) regions, then compared among the three conditions using two-way repeated measures ANOVA.

Results

The simultaneous DF had a significant effect on the IC amplitude, where the IC amplitude was significantly stronger under +7.50 D DF ($p < 0.01$) than in-focus condition, which was mostly contributed from the central and para-macular regions. No significant effect was observed in +2.50 D DF condition.

Conclusion

Under the effect of relatively strong simultaneous DF integration, the retina showed an enhanced retinal response, which was originated from the inner retina. Compared with peri-macular region, central and para-macular responses appeared to be more enhanced.

Introduction

Numerous studies have demonstrated that optical defocus actively regulates the outcomes of emmetropisation.[1] It is believed that there is a visual mechanism in the retina to detect imposed optical defocus and to provide feedback for the regulation of ocular growth. Consistent findings were shown across species, including chick,[2] tree shrew,[3] guinea pig,[4] mouse,[5] rhesus monkey,[6] and marmoset.[7] In general, for distant objects, a concave optical lens imposes hyperopic defocus, which accelerates the eyeball growth to become myopic, while a convex optical lens imposes myopic defocus, causing the eyes to become hyperopic by limiting the eyeball growth.

Previous studies have also shown that animal eyes could differentiate simultaneous optical defocus integration induced by dual-focus (DF) optical lens.[8-11] For example, the refractive end-point of chick eyes fell between the two optical powers of DF lenses.[11] McFadden and co-workers reported congruent findings in guinea pigs.[10] Human studies[12,13] using DF contact lens designs echoed the results of DF lens-induced refractive error changes in various animal studies. The rate of myopia progression was significantly slowed down by 30% in children who wore DF soft contact lenses.[12,13] Thus, the relative positive power component in the DF lenses was believed to have an effect on controlling myopia progression.

Multifocal electroretinogram (mfERG) is an objective functional test to detect localised electrical responses across the central retina (about 30° of the field). A modified paradigm, the global flash mfERG, added a global flash frame to the

conventional mfERG stimulation sequence in order to improve the measurement of the retinal response from the inner retina. The first-order kernel waveform of the global flash mfERG response contains direct and induced components. The direct component (DC) is a direct response to the focal flash, which mainly represents the outer retinal responses from cells including photoreceptor and bipolar cells.[14,15] The induced component (IC), which originates from the inner retina, is an adaptive effect induced by successive global flashes. The IC is derived mainly from the amacrine and ganglion cells.[14,15] Previous studies have shown that global flash mfERG in the human eye responded differently to myopic and hyperopic optical defocus induced by a single vision lens,[16,17] which was demonstrated to occur in the para-central retinal region. Therefore, the global flash mfERG response may be an important objective parameter to study the retinal mechanisms associated with emmetropisation. However, to date, there are no published studies determining the retinal activities of the human eye receiving simultaneous DF. This study aimed to investigate the changes in human electro-retinal activities measured by the global flash mfERG under the effect of different powers of simultaneous DF. Better understanding of the retinal physiological characteristics under simultaneous optical defocus, which is one of the current hypotheses in myopic control treatment, could facilitate the evaluation of the effectiveness of myopia control.

Methods

Subjects

Thirty adults (17 females) aged between 18 and 32 years with spherical equivalent refractive error between -1.50 and -5.50 D and astigmatism of 1.00 D or less in the right eye were recruited. Exclusion criteria were colour vision defect, history of epilepsy, ocular or systemic disease, myopia control treatment in the past 3 months, and abnormal visual acuity (best-corrected visual acuity worse than logMAR 0.00).

The study was approved by Human Subjects Ethics Committee of The Hong Kong Polytechnic University and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants after a detailed verbal explanation of the study. All participants had a comprehensive eye examination together with cycloplegic refraction, contact lens fitting, and mfERG measurement.

The right eye of the subjects was chosen as the tested eye. Two drops of 1% tropicamide (Alcon Laboratories, https://www.alcon.com/eye-care-products) were instilled to the tested eye. Cycloplegic subjective refraction was performed by an experienced optometrist adhered to maximum plus to maximum visual acuity (MPMVA) technique with duochrome test and +1.00 D blur test, on a computerised visual acuity chart mirrored 6 m away.[18] Astigmatism was checked using the Jackson-Cross-Cylinder technique with clustered dots as the non-directional target, firstly axis, then power, and then finally axis confirmation. MPMVA was re-confirmed after measuring astigmatism. The refractive

procedures were performed when the residual accommodation in three consecutive readings was less than 2.00 D, measured by the push-up method by the Royal Air Force ruler, after pupil dilation. The tested eye was then fitted with contact lenses based on the findings of cycloplegic subjective refraction and viewing distance of mfERG. The global flash mfERG measurements commenced 10 min after commencement of contact lens wear to allow for lens settling.

Study Design

In this cross-over study, the global flash mfERG in the tested eye of each subject was measured under three conditions: single vision contact lens (in-focus), +2.50 D DF contact lens (DFCL), and +7.50 D DFCL in random order. Each subject underwent mfERG measurements under all three conditions on the same day with a 45-minute washout period between each mfERG recording. For the power selection, +2.50 D DFCL was chosen because it is used in a commercially available myopia control product, while +7.50 D DFCL was chosen to understand changes of electro-retinal activities under simultaneous DF integration with a high positive defocus power.

Contact lenses

The DFCL was made of Efrofilcon A with a custom lathe cutting process. The lens had a water content of 74%, base curve of 8.3 mm, central thickness of 0.12 mm, lens diameter of 14.2 mm, modulus of 0.39 mPa, oxygen permeability of 60

Dk, and oxygen transmissibility of 75 Dk/t (at centre of a -3.00 D lens). Figure 1 shows the design of the DFCL. The DFCL was composed of two powers: one being the correction power of distance refractive error determined by cycloplegic subjective refraction and the second had relative myopic defocus power (+2.50 D and +7.50 D) compared to the correction power, which were arranged in a concentric ring design. The central portion was a 2.0 mm-diameter correction zone encircled by nine concentric rings (width 0.5 mm each) of alternating positive defocus and distance correction power. Biotrue One-day contact lens from Bausch & Lomb was selected as the control single vision contact lens, because of its lens parameters are similar to the DFCL: water content 78%, base curve 8.6 mm, central thickness 0.1 mm, lens diameter 14.2 mm, and modulus 0.42 mPa.

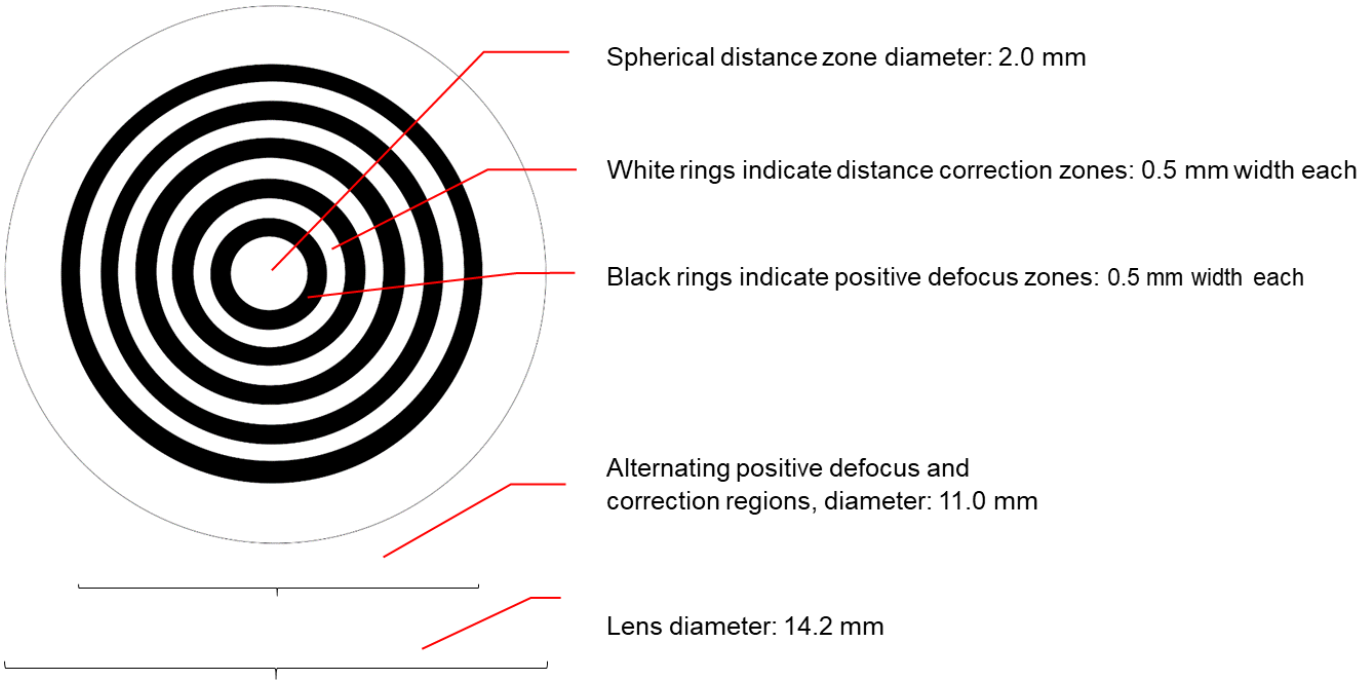


Figure 1. Design of the dual-focus soft contact lens

The contact lens power was calculated for each subject using the spherical equivalent refractive error at the corneal plane at an interval of 0.50 D (plus side preferred) to accommodate for the availability of the DFCL, corrected for the 67 cm viewing distance for mfERG stimulation display, which was the same for the single vision lens and the DFCL. For example, if the spherical equivalent power of cycloplegic subjective refraction at the corneal plane was -3.00 D, the chosen contact lens power was -1.50 D after correction of the viewing distance of mfERG stimulation. However, four subjects who had spherical equivalent power of -1.50 D at the corneal plane, resulting in a calculated contact lens power being plano. As plano power was not available for the single vision lens, a +0.25 D lens was used, whereas plano power was used for the DFCL. The contact lens fitting was evaluated after the lens had settled for at least 10 minutes. The contact lens fitting of ‘optimal fit towards the tight side’ was adopted to minimise any excessive decentration of the lens, which could affect the electroretinogram measurement. All subjects had no significant decentration of the tested contact lens exceeding 1 mm in the primary gaze or a lens movement exceeding 0.50 mm in the primary gaze during eye blinking.

Multifocal electroretinogram recording

The multifocal 103 non-scaled hexagonal stimuli generated from the Visual Evoked Response Imaging System (VERIS 6.0.6d19, https://www.veris-edi.com/) was presented at a high contrast level of 96% on a 24-inch colour liquid crystal display (S24E390HL, https://www.samsung.com/uk/support/model/LS24E390HL/EN/). The non-scaled hexagonal stimulus was used to minimise the possible interaction effect between the added defocus power and the spatial frequency (i.e. size) of the stimulus. Chin and co-authors[16] reported that the retina responded differently to stimuli with high and low spatial frequencies under optical defocus using global flash mfERG. The DC amplitude has a sign-dependent response to defocus under low spatial frequency, but this response was absent under high spatial frequency. The stimulus subtended 29° horizontally and 24° vertically at a working distance of 67 cm. The testing stimulus array was presented with a 2^{12} -1 pseudo-random binary m-sequence at a rate of 60 Hz. Each m-sequence stimulation cycle contained four frames: a multifocal flash frame (M; mean luminance: about 83 cd/m^2), a full screen dark frame (O; mean luminance: about 3 cd/m^2 per frame), a full screen global flash frame (F; mean luminance: about 166 cd/m^2), and a full screen dark frame (O) in each cycle. Each recording session lasted for about 9 min and was divided into 32 slightly overlapping segments, with each segment lasting for 17 s for better subject comfort. The measurement was conducted in a room environment with background illuminance of about 100 lux.

A Dawson-Tick-Litzkow (DTL) thread electrode placed behind the lower lid of the tested right eye acted as the active, a gold cup surface electrode positioned about 2 cm temporally from the outer canthus acted as the reference of the tested eye, and another gold cup surface electrode located at the central forehead acted as the ground. The pupil of the tested eye was dilated to at least 7 mm in diameter, while the untested eye was occluded during the measurement. The recorded retinal signals were amplified 100,000 times with a bandpass between 10 and 200 Hz (amplifier model: 15A54, https://www.veris-edi.com/). During the stimulation, the subject fixated on the red-cross target at the centre of the stimulus array without blinking. The fixation was monitored by the examiner using the real-time display of the VERIS system. Contaminated segments affected by blinks and eye movements were discarded and re-recorded.

Data analysis

The mfERG waveform was pooled and grouped into three concentric regions for analysis, i.e. central macular region (0°–8°), para-macular region (8°–18°), and peri-macular region (18°–30°), based on the mfERG studies by Chin and co-workers[16] and Ho and co-workers.[17] In the study by Ho and co-workers, the sign-dependent response to optical defocus was observed at 8°–30° retinal eccentricity, but not within the central 8° region. In the study by Chin and co-authors[16], the sign-dependent response to different spatial frequency under various optical defocus conditions was present at 11°–25° retinal eccentricity, but not within the central 11° region. In addition, Smith and co-workers[19] investigated

rhesus monkeys treated with a -3.00 D defocus lens with a central clear zone aperture. This central clear zone yielded 10º of unrestricted single vision, while 10º–31º eccentricity was affected simultaneously by both the -3.00 D annular lens and the unrestricted zone. Refractive status of the animals in this clear central-apertured lens group were comparable to those in the -3.00 D full-field lens groups, suggesting that the projection of defocus vision beyond the central 10º region effectively induced refractive changes. All these findings suggested that the para-macular retinal region was most likely the area of interest for detection of defocus. Therefore, ring 1 and ring 2 (within central 8º) defaulted by the VERIS system were pooled and classified as the central macular region for analysis. Rings 3–4 (8º–18º eccentricity) and rings 5–6 (18º–30º eccentricity) were pooled and classified as para-macular and peri-macular regions, respectively, based on the waveform characteristics as in previous studies.[16,17] Figure 2 shows the grouping of mfERG responses. Figure 3 shows a typical global flash mfERG waveform that yielded a direct component (DC) and an induced component (IC). The peak-to-trough amplitude of DC was the difference between the first major negative trough to first major positive peak, while the IC was measured from the second major positive peak to the second major negative trough. The peak time of DC was measured from the onset presentation of the stimulus to the first positive peak, while that of IC was the measured between the stimulation of the global flashes at 33.33 ms to the second major positive peak.

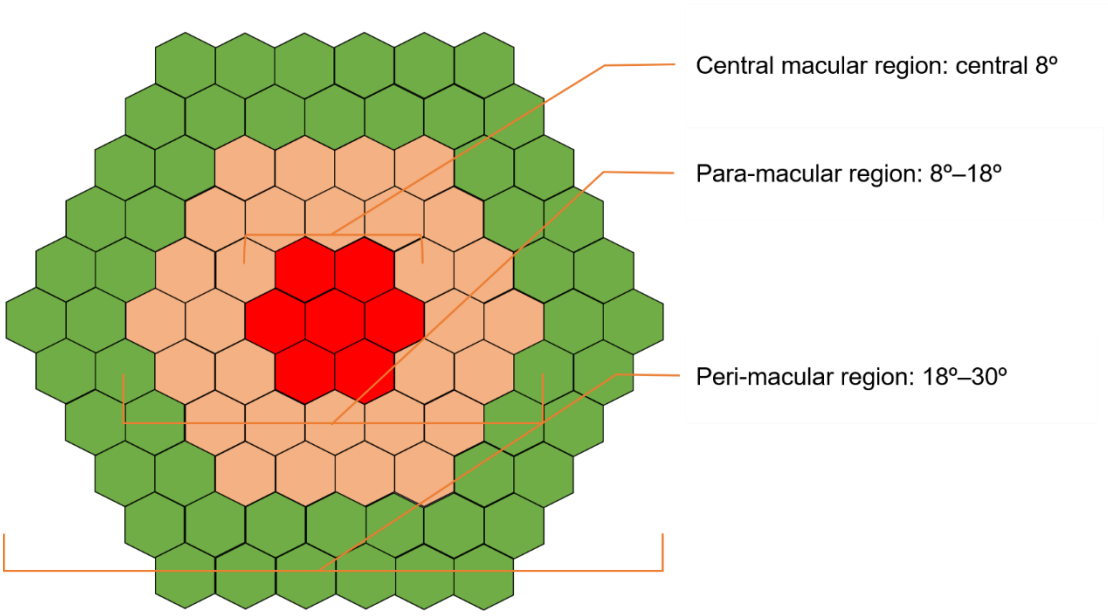


Figure 2. A schematic diagram of the grouping of mfERG responses

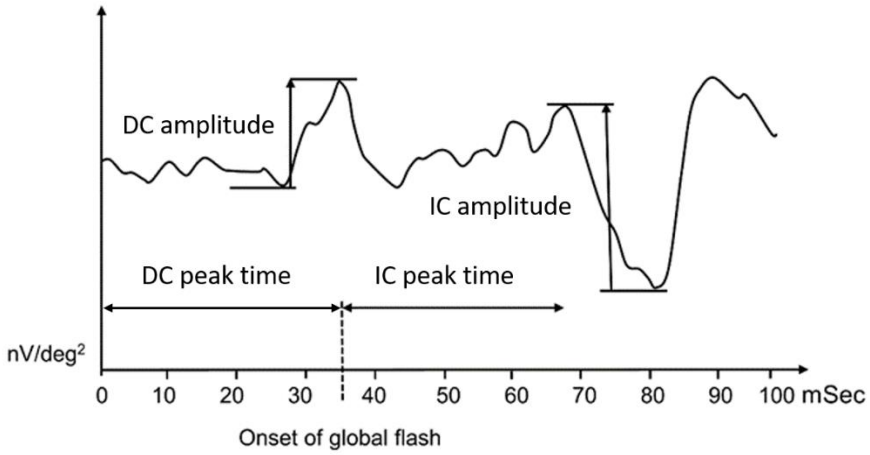


Figure 3. A schematic diagram of a global flash mfERG waveform with a direct component (DC) and an induced component (IC)

Statistical Analysis

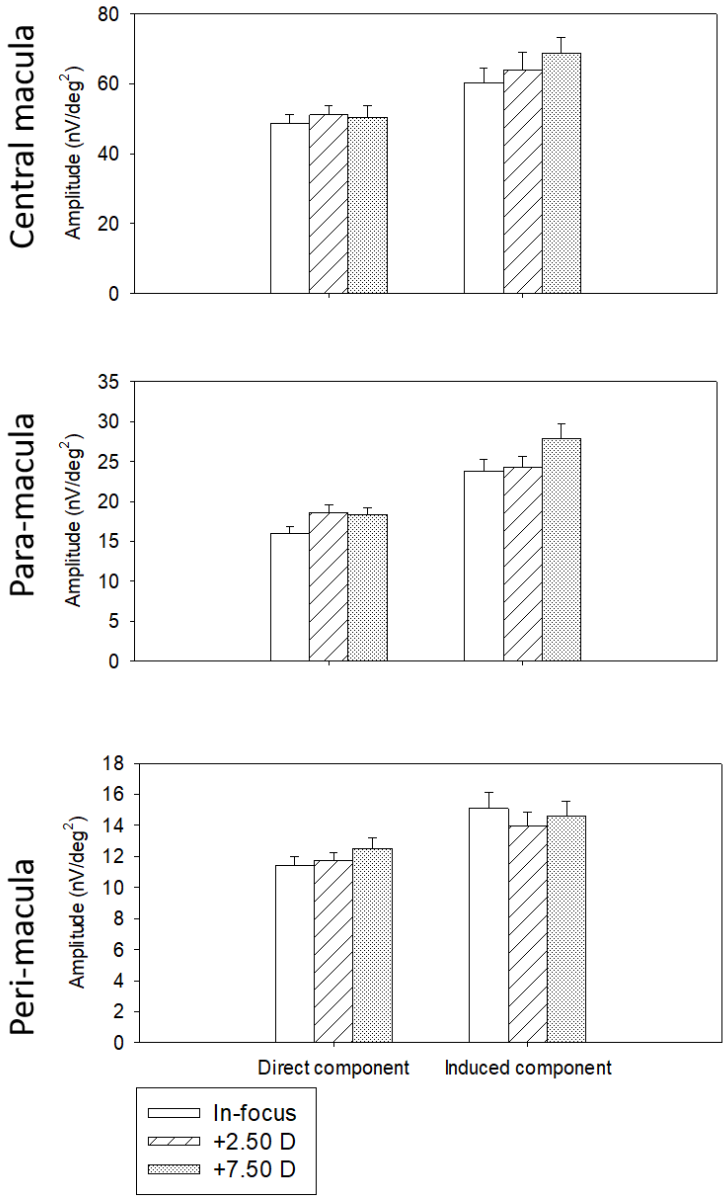
The data analysis was performed using the Statistical Package for the Social Sciences (SPSS 16.0.1, https://www.ibm.com/hk-en/analytics/spss-statistics-software). Two-way repeated measures analysis of variance (ANOVA) was used to analyse the main effect of defocus (in-focus, +2.50 D, and +7.50 D of DF) and retinal region, as well as the interaction effect (defocus x retinal region) on DC and IC amplitudes as well as peak times, using Bonferroni test for post-hoc comparisons. The assumption of sphericity was tested. If the assumption of sphericity was violated, the degrees of freedom were adjusted and the Greenhouse-Geisser tests were reported. The level of statistical significance was set as $p < 0.05$.

Results

The mean age of the 30 subjects was 23.1 ± 2.1 years (range: 19.7–31.4 years). The mean cycloplegic manifest refraction on the corneal plane and the best-corrected distance visual acuity (logMAR) were -3.21 ± 1.14D and -0.08 ± 0.02 (range: -0.10 to -0.04) respectively. The mean visual acuities were 0.06 ± 0.05 (range: -0.02 to 0.18) with +2.50 D DFCL and 0.06 ± 0.06 (range: -0.08 to 0.14) with defocus power of +7.50 D DFCL.

Amplitudes of global flash mfERG

Figure 4 shows the DC and IC amplitudes for different regions under various defocus conditions, which decreased with increasing eccentricity from the central macular to peri-macular regions. For the DC amplitude, the main effect of the retinal region was significant ($F_{1.08,28.92} = 292.66$, $p < 0.001$), but not for defocus ($F_{2,28 = 1.50}$, $p = 0.23$) or the interaction effect ($F_{2.19,27.81} = 0.31$, $p = 0.75$). For the IC amplitude, the main effect was significant for both defocus ($F_{2,28} = 4.61$, $p = 0.01$) and the retinal region ($F_{1.04,28.96} = 172.06$, $p < 0.001$), but the interaction effect was insignificant ($F_{2.11,27.89} = 2.18$, $p = 0.12$). Post-hoc comparison showed that the IC was significantly stronger under +7.50 D DF over in-focus condition (paired t-test with Bonferroni adjustment, $p < 0.01$), which appeared to be mostly contributed from central and para-macular regions as shown in Figure 4.



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253 **Figure 4. The mean direct component (DC) and induced component (IC)**

254 **amplitudes under different defocus conditions. Post-hoc comparison**

255 **showed a significant difference (p < 0.01) between in-focus and +7.50 D**

256 **conditions under the main effect of defocus**

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Peak times of global flash mfERG

Table 1 shows the DC and IC peak times for different regions under various DF conditions. For DC peak time, none of the main effect for defocus ($F_{2,28}$ = 2.34, p = 0.11), region ($F_{2,28}$ = 2.73, p = 0.07), nor the interaction effect ($F_{2.47,27.53}$ = 1.44, p = 0.24) was significant. For IC peak time, the main effect was significant for region ($F_{1.22,28.78}$ = 48.29, p < 0.001), but not for defocus ($F_{2,28}$ = 0.30, p = 0.73) nor the interaction effect ($F_{2.34,27.66}$ = 0.21, p = 0.84) was significant. However, no significant difference was observed in post-hoc comparisons.

Table 1. Summary of direct component (DC) and induced component (IC) peak times (mean ± SEM) under different defocus conditions

	Peak time (ms), Mean ± SEM		
Region	In-focus	+2.50 D DF	+7.50 D DF
DC			
Central macula (0° to 8°)	36.99 ± 0.45	36.60 ± 0.32	35.91 ± 0.43
Para-macula (8° to 18°)	36.24 ± 0.37	36.79 ± 0.30	36.08 ± 0.21
Peri-macula (18° to 30°)	36.14 ± 0.25	35.90 ± 0.20	35.87 ± 0.24
IC			
Central macula (0° to 8°)	37.62 ± 0.52	37.63 ± 0.47	37.61 ± 0.45
Para-macula (8° to 18°)	35.93 ± 1.38	35.70 ± 0.97	35.70 ± 0.93
Peri-macula (18° to 30°)	35.11 ± 0.20	35.10 ± 0.16	34.86 ± 0.19

Discussion

The results revealed that short-term exposure to simultaneous DF by DFCL significantly affected inner retinal responses of the global flash mfERG. The measurements showed that the IC amplitude significantly increased under the effect of simultaneous +7.50 D DF compared to the in-focus condition, mainly in the central and para-macular regions as observed in Figure 4. However, DC amplitude did not show significant difference among different DF conditions.

The current findings partially agreed with the results by Ho and co-workers,[17] who, using a positive defocus single vision lens instead of DFCL, demonstrated that IC amplitude was increased significantly at the para-macular region, but not central macular region. Also, they reported that the DC amplitudes at the para-macular region were not changed significantly by +2.00 D and +4.00 D mono-defocus. Previous animal studies also demonstrated differences in reactions to mono-defocus and simultaneous DF conditions. McFadden and co-workers[10] compared the refractive development of guinea pigs fitted with either a +5.00 D/0.00 D DF lens or +5.00 D full-field lens. The mean refractive response of the guinea pigs to the Fresnel lens was the weighted average of the response between the two constituent powers of the DF lens. Tse and co-workers[11] also showed the final refractive states of chicks, which wore a +10.00 D/-10.00 D DF lens, were positively biased between the two constituent powers of full-field +10.00 D and -10.00 D optical lenses. In the study by Ho and co-workers,[17] the optical defocus was mono-defocus which involved one focal plane, whereas the current study applied DFCL involving two focal planes competing with each

other. Therefore, it could be one of the reasons that a significant difference was not observed in +2.50 D DF condition. However, Chin and co-authors[16] found that the DC amplitude was increased significantly by approximately 20% under +2.00 D mono-defocus condition. The reason for such discrepancy may be the incorporation of spatial frequency gratings into the mfERG stimulus in their study, which differs considerably from the regular global flash mfERG.

Compelling evidence from animal studies[8,10,11] has shown that the retina could decode and process different signs and magnitudes of the opposing defocus signals simultaneously induced by DF lenses. The processed signals mediated ocular growth to reach a final refractive state, which was between the two focal planes. Recently, it has been proposed that the peripheral retina is important for regulation of ocular growth due to the induced defocus, which occurred even if the central retina was laser ablated or without any optical defocus.[19-22] However, it appears that the central retina also plays a role in axial ocular growth, as ocular growth in chick could be manipulated by adjusting the size of the central form deprived zone.[23] Our results suggested the enhanced inner retinal response in the central and para-macular regions under +7.50 D DF condition may reflect these two regions are involved in the detection of defocus induced by DFCL. Furthermore, the electrophysiological study by Li and co-workers[24] showed that central inner retinal activity, in terms of IC amplitude, is inversely related to myopia development. Whether this enhanced central inner retinal response by the DFCL contributes to its myopia control effect[12,13] warrants further study.

The design of DFCL created two image focal shells over the retina. The directional sensitivity of the photoreceptors perceiving the light rays through the DFCL may differ from the in-focus contact lens, i.e. creating different level of Stiles-Crawford effect. However, further study will be needed, as it is unclear whether the DFCL would increase the directional sensitivity of the photoreceptors, which may vary the retinal illuminance and thus the mfERG amplitude. It may be also argued that the changes of the IC amplitude were caused by the degradation of the image contrast of the optical defocus, rather than the effect of simultaneous DF integration. However, decreased contrast or luminance of the visual stimuli has been reported to reduce the amplitude of mfERG response,[25-27]which is in contrast to the findings of increased IC amplitude in the current study. Therefore, the increased IC amplitude is likely to be attributable to the visual signal being mediated by simultaneous DF integration.

The central and para-macular regions were most affected by simultaneous DF stimulation. Previous studies related to electrophysiological activities on optical mono-defocus reported sign-dependent changes.[16,17,28] In particular, Khanal and co-workers[28] recently demonstrated the IC amplitude was higher under positive defocus than in-focus and negative defocus with or without short-term administration of 0.1% atropine, which has been shown to be an effective myopia control regimen.[29-31] They have also demonstrated a differential effect on the IC amplitude region under different signs of defocus, whereby atropine increased IC amplitudes under positive defocus, but not under negative defocus.

A recent study by Turnbull and co-workers[32] investigated the relationship between uncorrected peripheral refractive error and global flash mfERG. Although the peak time was consistent, their findings on the DC and IC amplitudes appeared different from those of the current study. It is worth noting that there are several differences between the studies. Firstly, their methodology of "controlling" retinal defocus was to recruit subjects with a wide range of refractive errors, while in the current study, mfERG of the same subjects was compared with different contact lenses. Secondly, only six hexagons from paracentral region of different meridians were analysed in their study. As the ERG response drops significantly with increasing eccentricity, results from hexagons of the same eccentricity were analysed in our study to maximise the signal-to-noise ratio. It is also recognised that there is a regional effect on peripheral refractive error, as well as the mfERG responses, which could be minimised by obtaining results from the ring analysis. Finally, the DFCL used in the current study would create two image shells (i.e. in-focus and myopic defocus) on the retina. This possibly triggers an integrated activity due to two focal shells, which is different from the uncorrected defocus in the study by Turnbull and co-workers.[32]

There are several limitations in the current study. The actual retinal defocus in the three regions experienced by the individuals was not measured. The lens power of DFCL in 0.50 D increments might not exactly match the spherical equivalent of refractive errors in each subject. However, the use of more plus power chosen to the nearest 0.50 D increment would help to minimise the

residual accommodative response. In addition, only the effect of +2.50 D and +7.50 D defocus power on the electro-retinal activities was investigated. It would be preferable to observe the trends in electro-retinal activities under DFCL with additional steps. Furthermore, the images overlapping induced by the dual powers (in-focus and myopic defocus) from the DFCL may affect the interpretation of the results. Firstly, the image of the stimuli formed by the myopic defocus from DFCL would be different from that formed by the in-focus image from DFCL in terms of the retinal image size. This would cause the shifting of the boundaries of the stimulus region, which may affect the mfERG response. In addition, this shifting of the boundaries may also make the ring analysis less appropriate for comparison of the results. Secondly, the overlapping of stimulation caused by two different focal shells may have influenced the cross-correlation between the m-sequence algorithm and the mfERG responses. In order to minimise the possible influence due to the image overlapping induced by DFCL, the hexagon grouping was modified from six rings to three annular regions in the analysis. As each region covers more retinal area than those originally defaulted by the VERIS system, the effect of boundary shifting and image overlapping would be lower than the analysis applied on the small retinal region. Our results also indicated that the inner retinal response was affected by the DF, which appeared mainly in the central and para-macular regions but not in peri-macular region. As the spatial resolution of the retina peaks at the central region, which may magnify the neuronal response to the alteration of the retinal image size over the peripheral retina. Whether this phenomenon is due to the

smaller receptive field size in the central retina, or the retinal image properties by the DFCL warrants further studies.

Conclusion

The DFCL produced in-focus and myopic defocus retinal images simultaneously and triggered nearly instantaneous changes in electro-retinal activities. Predominantly, the inner (IC) electro-retinal activities reacted to relatively large magnitude of simultaneous optical defocus integration induced by DFCL. Generally, the simultaneous optical defocus integration would be expected to modulate activities at different retinal levels with respect to defocus power. Further studies on retinal activities under different myopia control treatments, such as orthokeratology and defocus incorporated multiple segments (DIMS) lens, are necessary to confirm our findings.

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