



# Selective i-wave attenuation in unilateral high myopia

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## Abstract

**Significance** Bipolar cell activity plays a crucial role in myopia development. The light-adapted electroretinogram has its photoreceptor (a-wave) and post-receptor (mainly b-wave) origins with a later i-wave component primarily representing the activation of the OFF-bipolar cells. It has been proposed that retinal OFF-pathway alteration may contribute to the development of myopia. Therefore, elucidating specific electroretinography (ERG) changes in individuals with unilateral high myopia (UHM) could contribute to understand the underlying pathomechanisms of myopia development and devise targeted treatment options.

**Purpose** This study aimed to compare light-adapted ERG waveforms between low-myopic/emmetropic and highly myopic eyes in patients with UHM eyes

sharing an identical genetic blueprint. The subsequent comparison of the responses between highly myopic and healthy fellow eyes aimed to investigate possible photoreceptor and/or post-receptor pathway alterations that may play a role in myopic refractive errors.

**Methods** Ophthalmological and electrophysiological examinations were carried out in four individuals with UHM [mean interocular difference in spherical equivalent:  $10.12 \pm 2.7$  (7–13.5) D]. ISCEV standard light-adapted electroretinograms were recorded from both eyes using LKC RETeval® portable ERG unit and DTL electrodes under pupil dilation.

**Results** The results showed comparable a- and b-wave amplitudes with consistently reduced i-wave amplitudes in the highly myopic eyes compared to the lower- or non-myopic fellow eyes.

**Conclusion** These findings suggest that, beyond genetic susceptibility and in the absence of overt unilateral ocular pathology, additional modulatory influences may contribute to the localized retinal regulatory mechanisms. Moreover, the i-wave appears to be a promising electrophysiological biomarker capable of detecting subtle alterations in retinal signaling, with potential implications for elucidating myopia pathogenesis and guiding targeted therapeutic development.

**Keywords** Retinal signaling asymmetry · Unilateral high myopia (UHM) · Electroretinogram · OFF-pathway · Photopic i-wave

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## Introduction

The global myopia epidemic has shown a rapid and substantial increase in recent years [1]. Due to their vision-threatening complications, extreme phenotypes of myopia, specifically high and pathological myopia, represent a significant public health and economic burden [2, 3]. This highlights the urgent need to elucidate pathomechanisms and advancing targeted treatment strategies in this field.

Unilateral high myopia (UHM) serves as a valuable model for myopia research, as it allows for the study of fellow eyes with differing growth patterns while sharing the same genetic background [4, 5]. This condition may provide insights into the mechanisms underlying asymmetric ocular growth and the disparate refractive development that leads to an extreme phenotype in only one eye. Refractive development is unique in that it is primarily regulated by local retinal mechanisms rather than central neural mechanisms [6]. Light exposure and retinal phototransduction play a critical role, making it rational to investigate differences in local retinal pathomechanisms that may underlie the asymmetric refractive development of fellow eyes. Light modulates refractive eye development via dopaminergic neuromodulatory mechanisms mediated through parallel ON–OFF retinal signaling [7]. A balanced function of these parallel pathways is essential for normal refractive development [8–10].

The i-wave of the photopic ERG represents the activity of the cone-driven retinal OFF pathway [11–13]. The i-wave has recently gained attention in myopia research, recent findings identifying it as a valuable electrophysiological biomarker associated with genetic factors and functional mechanisms involved in myopia development [14]. Given the emerging recognition that differential pathway activity may drive eye-specific growth patterns, this study aimed to further characterize how functional alterations in cone-driven signaling relate to the development of unilateral extreme myopia.

## Methods

All procedures were performed in accordance with the Declaration of Helsinki (1964) and its later amendments or comparable ethical standards. The study protocol was approved by the Regional

Scientific and Research Ethics Committee (ETT RKEB, registration number: DE RKEB/IKEB 7115-2025). Written informed consent was obtained from all participants or their legal guardians (as most participants were children under 18 years of age).

## Patients

Patients with UHM were included, provided that the myopia was primarily axial in origin and not attributable to corneal or lenticular causes. Exclusion criteria comprised any unilateral ocular or neurological structural abnormalities that could explain excessive axial elongation in one eye (such as optic nerve hypoplasia, macular hypoplasia, coloboma, retinopathy of prematurity, or facial dysmorphism), as well as a family history of high myopia.

Prior to patient examinations, a trial recording was obtained from the right eye of a healthy 25-year-old female volunteer. The resulting ERG waveform is presented in Fig. 2.

## Ophthalmological examinations

UHM was identified as high myopia ( $\leq -6.0D$ ) in one eye and at least 5.0D difference in spherical equivalent (SE) between the contralateral eyes.

Patients' own medical history including any associated unilateral ocular or neurological disorder as well as their family history for myopia were collected. Best corrected visual acuity (BCVA) was monocularly measured with the decimal chart. Slit lamp biomicroscopy and fundus ophthalmoscopy under mydriasis were carried out with Topcon SL-D701 (Topcon, Tokyo, Japan). Refractive errors were measured under cycloplegia, and were expressed as SE. Axial length (AL) were measured using IOLMaster 700, a swept-source OCT-based optical biometry device (Carl Zeiss Meditec AG, Jena, Germany). Ultrasound B images were taken to illustrate differences in eye shape between fellow-eyes with Accutome 4Sight (Accutome Inc., Malvern, PA). Ultra-wide field (200°) fundus images (Optos® California, Optos, Marlborough, MA) were taken from each eye of the patients. Fundus appearances were assigned according to the META-PM (meta analyses of pathological myopia) classification system [15].

## Electrophysiology testing

Bilateral ISCEV standard light-adapted (photopic) electroretinograms (ERGs) were recorded using the RETeval® portable ERG device (LKC Technologies, Gaithersburg, MD, USA) [16]. Prior to recording, all participants underwent pupil dilation with 1% tropicamide eye drops (Unitropic® 10 mg/ml), achieving maximal mydriasis for standardized retinal illumination. A corneal fiber electrode was used as the active electrode and positioned along the lower conjunctival fornix of each eye. Reference electrodes were placed at the ipsilateral outer canthus, and a ground electrode was positioned on the forehead, following the manufacturer's recommended placement protocol. LA ERGs were recorded following a minimum of 10 min of photopic adaptation to a steady background luminance. To ensure a high signal-to-noise ratio, each recorded response consisted of the average of 30 individual sweeps. The recording epoch was set to 120 ms, providing a sufficient temporal window to capture the late-phase i-wave component. Participants were seated comfortably in a dimly lit room, instructed to fixate on the device's fixation target, and to avoid blinking during stimulus presentation. Bilateral recordings were performed sequentially for the right and left eyes. A standard flash intensity of 3 cd·s/m<sup>2</sup> was delivered on a white background luminance of 30 cd/m<sup>2</sup>. Artifact rejection was performed in real-time using the manufacturer's integrated software criteria. The final averaged signals were used for subsequent analysis.

Signals were amplified, filtered and averaged according to the device's automated protocol. Time-domain analysis was applied to extract a-wave, b-wave and i-wave. Peak-to-peak amplitudes and implicit times were measured automatically, and traces were reviewed for quality control. Data from both eyes were collected under identical conditions to allow for direct bilateral comparison.

A- and b-wave parameters were automatically extracted using the LKC Technologies RFF Extractor software, whereas i-wave amplitudes were determined separately, as this component was not included in the software's standard automated output. Waveforms were first qualitatively inspected to verify the presence of a discernible i-wave. Subsequently, the i-wave trough-to-peak amplitude was calculated in Microsoft Excel using predefined functions

to identify the minimum and subsequent maximum values within the selected post-b-wave time window (40–55 ms). The i-wave amplitude was then defined as the voltage (in µV) difference between the preceding negative trough (following the b-wave peak) and the maximum positive excursion of the i-wave. This approach minimized subjective bias associated with manual cursor placement and ensured standardized, reproducible measurements across recordings.

## Statistical analysis

Due to the small sample size ( $n=4$  pairs), effect size descriptors (Cohen's  $d_z$ ) and their 95% confidence intervals (CI) were utilized to evaluate the magnitude of differences between highly myopic and control eyes. To evaluate whether the i-wave reduction was selective, i.e. disproportionate to the a- and b-wave alterations; the per-eye HM/FE amplitude ratios for the a-, b- and i-waves were computed, Cohen's  $d_z$  on the raw paired differences was calculated, and the effect sizes were compared.

## Results

Table 1 summarizes the clinical characteristics of the four UHM patients investigated. The mean difference in AL and SE between patients' contralateral eyes were  $3.135 \pm 1.28$  mm, and  $10.12 \pm 2.7$  D, respectively. High myopia was primarily of axial origin,

**Table 1** Demographic, ophthalmology and electrophysiology/i-wave results of patients

|        | Age (years) | SE (D of myopia) | AL (mm) | BCVA (decimal) | i-wave amplitude (µV) |
|--------|-------------|------------------|---------|----------------|-----------------------|
| P1-HM  | 9           | 7                | 24.02   | 0.6            | 1.9                   |
| P1- FE | 9           | 0                | 21.91   | 1.0            | 10.7                  |
| P2-HM  | 12          | 11               | 26.3    | 0.08           | 8.92                  |
| P2- FE | 12          | 3                | 24.34   | 0.4            | 13.65                 |
| P3-HM  | 9           | 12               | 27.05   | 0.1            | 10.44                 |
| P3- FE | 9           | 0                | 23.01   | 1.0            | 19.45                 |
| P4-HM  | 24          | 16               | 28.76   | 0.6            | 6.5                   |
| P4- FE | 24          | 2.5              | 24.33   | 1.0            | 10.39                 |

P1–4: patients 1–4, HM: highly myopic eye, FE: fellow eye, SE: spherical equivalent, AL: axial length, BCVA: best corrected visual acuity

corneal and lens powers of patients' both eyes were in normal range.

The mean BCVA (decimal) of the highly myopic eyes was  $0.345 \pm 0.29$  (0.08–0.6), compared to  $0.85 \pm 0.25$  (0.4–1.0) in the fellow eyes. The reduced visual acuity in affected eyes may reflect anisometropic amblyopia, as no structural abnormalities were evident. Representative fundus images and ultrasound B-scan findings from a patient with unilateral high myopia are shown in Fig. 1.

The initial components, represented by the a-wave (primarily photoreceptor initiated off-bipolar cell activity) and b-wave (primarily on- and off-bipolar cell activity), demonstrated high stability across both study eyes. Furthermore, the mean values were comparable to results from a healthy control (a-wave amplitude =  $23.47 \mu\text{V}$  and time = 12.86 ms, b-wave amplitude =  $112.23 \mu\text{V}$  and time = 28.52 ms) which traces are shown in Fig. 2. Specifically, the mean a-wave amplitude was  $26.1 \pm 8.8 \mu\text{V}$  in highly myopic eyes compared to  $20.4 \pm 8.2 \mu\text{V}$  in non-(high) myopic eyes. Similarly, b-wave amplitudes remained comparable, with mean values of  $93.0 \pm 9.2 \mu\text{V}$  and  $101.3 \pm 17.1 \mu\text{V}$ , respectively (Fig. 3).

To assess differences in myopia severity parameters (AL, SE), visual acuity (BCVA) and the i-wave

amplitude between the highly myopic and low myopic/emmetropic fellow eyes of patients, effect size descriptors were used. All parameters demonstrated 100% directional concordance across the pairs. For the i-wave the mean interocular difference was 6.61, yielding a large effect size ( $d_z = 2.47$ ). These findings indicate a consistent and substantial physiological reduction of the i-wave in highly myopic eyes (Table 2).

A reduction in the light-adapted (LA) ISCEV standard ERG i-wave amplitude in highly myopic eyes relative to the fellow (low-myopic/emmetropic) eyes is shown in Fig. 2. The i-wave, which follows the b-wave in the LA flash ERG, is believed to originate mainly from activity of the inner retina (bipolar-ganglion cell interactions), and is attenuated in eyes with axial elongation. Since high myopia is associated with retinal stretching, thinning of the inner retinal layers, and potential disruptions in synaptic connectivity, these changes may reduce the efficiency of signal transmission through the cone-driven pathways, leading to diminished i-wave amplitude. The observed i-wave reductions in the highly myopic eyes are consistent with functional deficits secondary to myopia-induced retinal remodeling rather than generalized photoreceptor dysfunction, as earlier ERG

**Fig. 1** Optos fundusphotography and Ultrasound B of Patient 3. **A.** Optos fundusphotography (Optos® California) reveals normal retina in the emmetropic right eye (OD), and incipient myopic pathological alterations (tessellated retina, peripapillary chorioretinal atrophy) in the highly myopic left eye (OS) of a UHM patient (12.0D difference between contralateral eyes). **B.** Ultrasound B image (Accutome 4Sight) shows normal axial length and eye shape in the emmetropic OD, while increased axial length and incipient posterior staphyloma in the highly myopic OS. OD: right eye; OS: left eye, SE: spherical equivalent, AL: axial length, BCVA: best corrected visual acuity

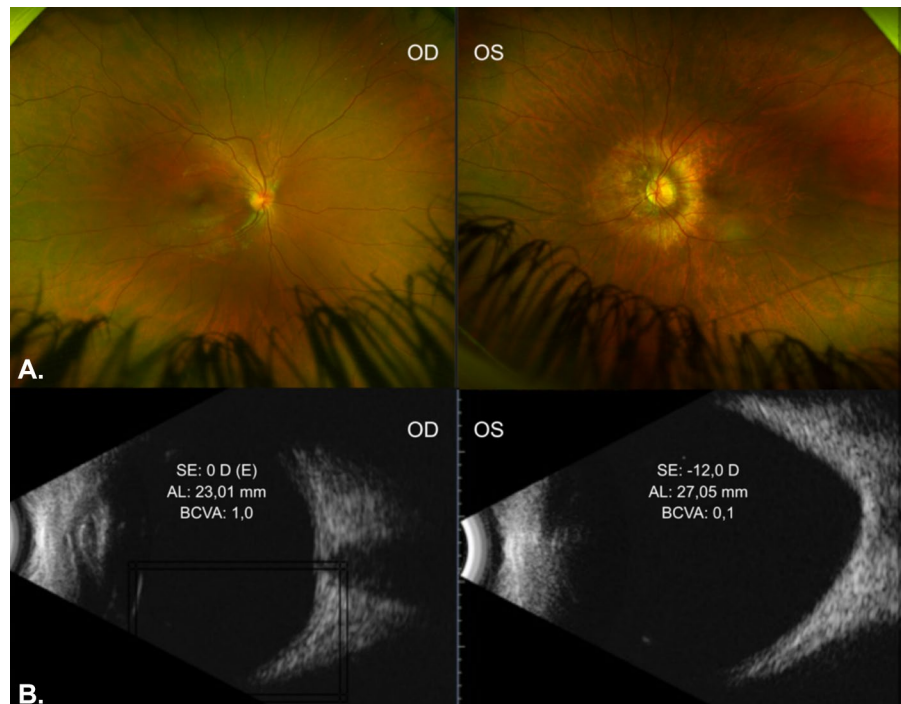
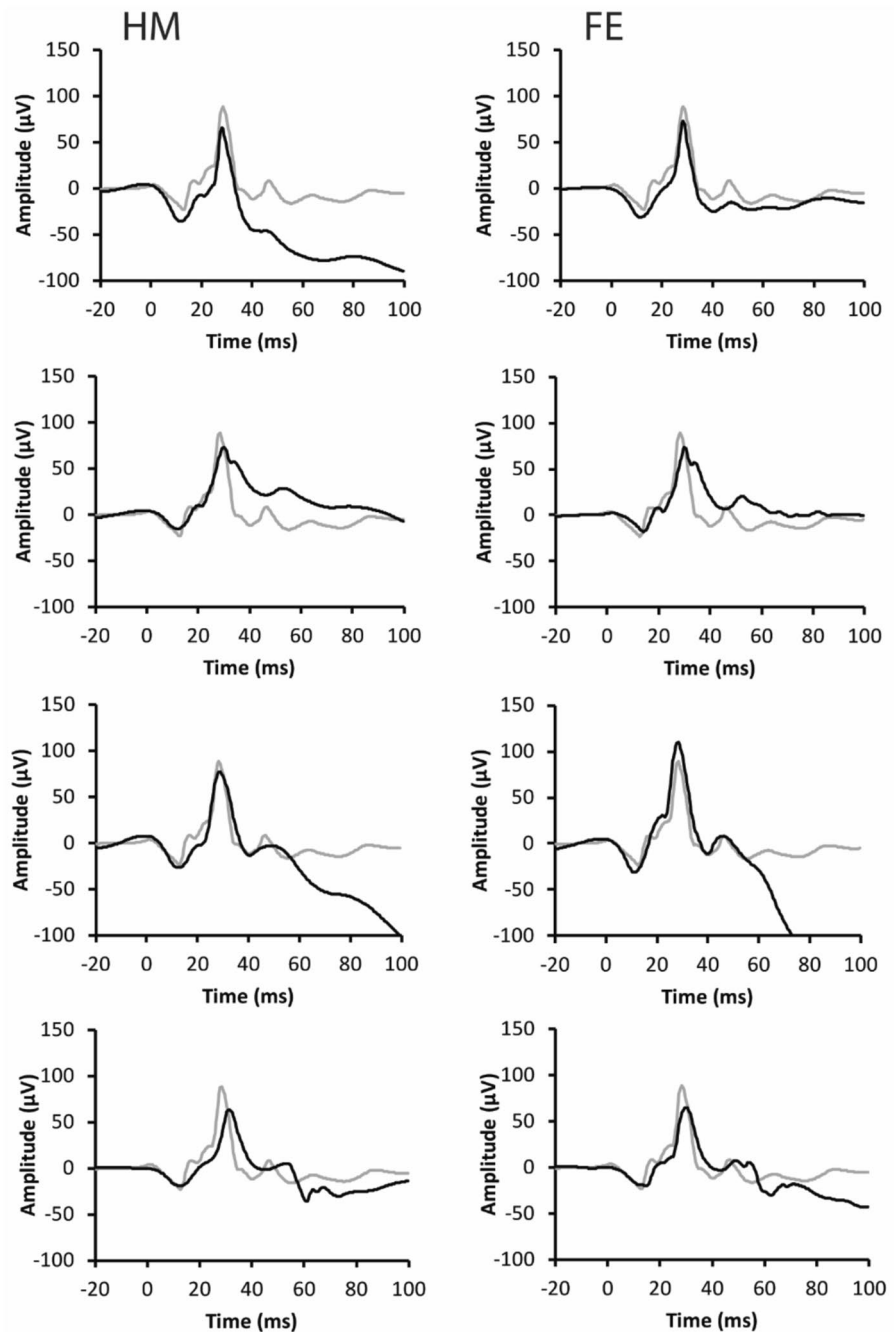


**Fig. 2** Averaged light-adapted ERG waveforms recorded from the highly myopic (HM) and fellow eyes (FE) of patients with unilateral high myopia. In each plot, a control trace of a healthy 25-year-old female volunteer is shown in grey to facilitate visual comparison with the patient-derived responses. HM: highly myopic eye; FE: fellow eye



components (a- and b-waves) remained relatively preserved (Fig. 3 ).

To evaluate whether the reduction of the i-wave in highly myopic (HM) eyes was selective or merely proportional to a generalized retinal depression, we calculated and compared the HM/FE amplitude

ratios and paired-sample effect sizes (Cohen's  $d_z$ ) of the a-, b-, and i-waves. The data are presented in Table 3.

As shown in Table 3, the data strongly support the selectivity claim:

**Fig. 3** Bar plots comparing the mean amplitudes and implicit times of the a-wave, b-wave, and i-wave between highly myopic (HM: grey bars) and fellow eyes (FE: grey white bars) in patients with unilateral high myopia. HM: highly myopic eye; FE: fellow eye

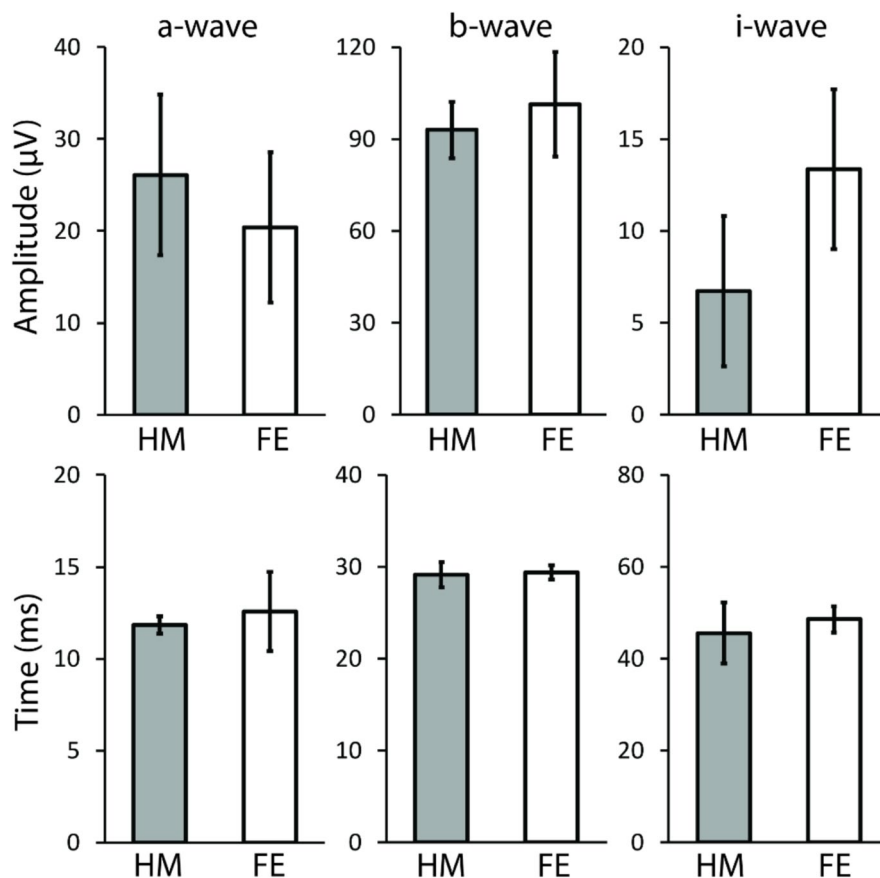


**Table 2** Paired-sample statistical parameters and effect sizes for highly myopic and low myopic/emmetropic eyes (n = 4 pairs/8 eyes)

| Parameter        | Mean difference ( $\Delta$ ) | SD of difference ( $SD_{\Delta}$ ) | Cohen-d ( $d_z$ ) and 95% CI | Group with higher value |
|------------------|------------------------------|------------------------------------|------------------------------|-------------------------|
| i-wave amplitude | 6.61 $\mu$ V                 | 2.68                               | 2.47 [0.50–4.44]             | LM/E (FE control)       |
| AL               | 3.14 mm                      | 1.30                               | 2.41 [0.44–4.35]             | HM                      |
| SE               | 10.13 D                      | 3.15                               | 3.22 [0.75–5.64]             | HM                      |
| BCVA             | 0.51 (decimal)               | 0.26                               | 1.95 [0.25–3.62]             | LM/E (FE control)       |

AL: axial length, SE: spherical equivalent, BCVA: best corrected visual acuity, HM: highly myopic, LM: low myopic, E: emmetropic, FE: fellow eye, CI: confidence interval

**Table 3** Selectivity analysis comparing a-wave, b-wave, and i-wave amplitudes (n = 4 pairs)

| Wave type | HM/FE | Mean difference | Cohen-d ( $d_z$ ) | 95% CI          | Directional concordance |
|-----------|-------|-----------------|-------------------|-----------------|-------------------------|
| a-wave    | 1.30  | −3.90 $\mu$ V   | 0.51              | [−0.53 to 1.55] | No (2/4 pairs)          |
| b-wave    | 0.94  | 7.04 $\mu$ V    | 0.82              | [−0.31 to 1.95] | Yes (4/4 pairs)         |
| I-wave    | 0.49  | 6.61 $\mu$ V    | 2.47              | [0.5 to 4.44]   | Yes (4/4 pairs)         |

HM: highly myopic, FE: fellow eye, CI: confidence interval

1. Amplitude ratios: In HM eyes, the i-wave amplitude was reduced to an average of 49% of the fellow control eye's value (a ~51% reduction). In contrast, the outer retinal components remained largely preserved, with the b-wave showing only a minor 6% reduction (mean ratio: 0.94) and the a-wave showing no systematic reduction (mean ratio: 1.30).
2. Effect sizes: The paired-sample effect size for the i-wave reduction ( $d_z=2.47$ ) is robust and larger than the effect sizes for the b-wave ( $d_z=0.82$ ) and the a-wave ( $d_z=0.51$ ).

These findings provide quantitative evidence that the i-wave reduction is disproportionate to the relatively preserved outer retinal responses (a- and b-waves).

## Discussion

Photopic ERG i-waves were recorded according to ISCEV standards under light-adapted conditions. In all four cases of unilateral high myopia, i-wave amplitudes were consistently reduced in the highly myopic eyes compared with their fellow eyes, while a- and b-waves remained relatively preserved. This preservation of early ERG components suggests that the observed variability in the later i-wave likely reflects specific alterations in the inner retinal circuitries, rather than a generalized deficit in outer retinal processing.

Retinal pathways involved in myopia development have been studied extensively, whereas i-waves in this context have only recently gained attention [14]. The i-wave is a less studied component of the light-adapted electroretinogram compared to the classical a- and b-waves, appearing as a smaller positive deflection following the b-wave. While the a- and b-waves primarily reflect the activity of the photoreceptors and ON-bipolar cells, respectively, the i-wave is believed to arise mainly from cone-driven OFF pathways, and to represent the activity involving bipolar cells and other proximal inner retinal elements, such as amacrine cells.

The i-wave was originally identified by Cobb and Morton in 1952 [11], and further characterized by Nagata in 1962 [12]. Subsequent pharmacological studies in primates by Rangaswamy et al. confirmed

its origin in the OFF pathway and located it to a stage distal to the ganglion cells, within the inner retinal layers [11–13]. At the same time, altered signaling in the retinal OFF pathway has been proposed to contribute to the development of myopic refractive error [9, 17, 18].

Similar observations have been reported in glaucoma, where significant changes in the i-wave and other OFF-related components were found despite relatively preserved a- and b-wave responses, and experimental studies in primates have also demonstrated reduced OFF-responses, including decreased i-wave amplitudes under elevated intraocular pressure [19, 20]. Furthermore, clinical studies suggest that i-wave-related ERG parameters may provide additional information on inner retinal function and contribute to the assessment of retinal ganglion cell-related dysfunction beyond conventional markers such as the photopic negative response (PhNR) [21].

The only recent study examining the photopic ERG i-wave in the context of myopia has highlighted the significant association of i-wave amplitudes with allelic dosage at the GJD2 myopia risk locus, indicating a functional relationship between this genetic variant and OFF-pathway retinal signaling in myopia development [14].

Unilateral high myopia, defined as a difference of 5 or more diopters between the two eyes, is a rare form of myopic anisometropia, where high myopia develops in one eye while the fellow eye remains less myopic or emmetropic. Axial elongation is the primary cause of high myopia rather than refractive changes of the cornea or the lens. The myopic eye is typically 2.5–4 mm (average: 3.3 mm) longer than the fellow eye, leading to significant refractive error difference [4, 5]. This condition is relatively frequently linked to unilateral ocular or neurological structural anomalies responsible for excessive axial elongation on one side, including optic nerve hypoplasia, macular hypoplasia, coloboma, retinopathy of prematurity, and facial dysmorphism. Such abnormalities are often the cause of decreased visual acuity in the affected eye [5, 22]. Nevertheless, visual acuity in the highly myopic eye may be further compromised due to anisometropic amblyopia, a frequent complication associated with UHM [23, 24].

While unilateral high myopia shares the complex genetic-environmental etiology of bilateral high myopia, genetics likely plays a more subtle role compared

to typical bilateral myopia, as UHM occurs despite similar genetic and environmental influences affecting both eyes [25]. Furthermore, genetic defects underlying UHM are less well known than those associated with typical high myopia.

In this study, we aimed to utilize this unique condition, where only one eye develops high myopia despite a shared genetic background, to investigate alterations in the retinal ON and OFF pathways associated with myopic refractive error.

Although the control fellow eyes were not entirely uniform with respect to refractive error (including both emmetropic and low-myopic eyes), they can be considered electrophysiologically homogeneous. In contrast to high myopia, which is regarded as a pathological condition and is associated with a higher prevalence of ERG abnormalities due to excessive retinal stretching [26], low myopia is generally considered physiological from an electrophysiological perspective. In eyes with refractive values less negative than the  $-3$  D threshold, axial elongation is typically small ( $<1$  mm), resulting in minimal mechanical stretching of the eye and, consequently, no appreciable ERG alterations compared with emmetropic eyes [27]. Therefore, despite some variation in refractive status, the control eyes may reasonably be considered a homogeneous reference cohort for electrophysiological analyses [27].

In all four cases presented, effect size descriptors demonstrated 100% directional concordance across the pairs and an exceptionally large effect size, together indicating a consistent and substantial physiological reduction of the i-wave in highly myopic eyes.

To evaluate whether the reduction of the i-wave in highly myopic (HM) eyes was selective or merely proportional to a generalized retinal depression, we compared the HM/FE amplitude ratios and paired-sample effect sizes (Cohen's  $d_z$ ) of the a-, b-, and i-waves. The mean HM/FE amplitude ratio for the i-wave represented a substantial average reduction of 51% in HM eyes relative to fellow control eyes. In contrast, the mean HM/FE ratio for the b-wave represented a minor reduction (6%), while for the a-wave there was systematic no reduction. Furthermore, Cohen's  $d_z$  calculations on interocular differences revealed that the effect size for the i-wave reduction ( $d_z=2.47$ ) was substantially larger than those observed for the outer retinal components- the b-wave ( $d_z=0.82$ ) and the

a-wave ( $d_z=0.51$ ). These objective metrics demonstrate that the physiological depression of the i-wave in HM eyes is highly selective and disproportionate to the relatively preserved outer retinal responses (a- and b-waves).

Oculomotor instability in the highly myopic (amblyopic) eyes should be considered a potential confounding factor of our measurements. Patients with amblyopia and reduced visual acuity may exhibit unstable fixation, including increased drift and microsaccadic activity, which could affect waveform consistency. However, this factor is unlikely to have substantially influenced the i-wave attenuation observed in the present study. Full-field ERG reflects a global retinal response elicited by diffuse Ganzfeld stimulation and does not critically depend on precise foveal fixation. Furthermore, the ISCEV standards recommend fixation monitoring during recordings [16], which was performed throughout the entire acquisition period in this study. Nevertheless, abnormal fixational eye movements may still have contributed to the attenuation or asymmetry of the i-wave amplitude and this should be acknowledged as a potential confounding factor when interpreting the findings.

The unilateral nature of our findings provides a robust internal control that strengthens our interpretation. Given that both eyes share an identical genetic background, the localized attenuation of the i-wave specifically in the highly myopic, amblyopic eye argues against a purely systemic or hereditary genetic etiology causing inner retinal dysfunction. Instead, this discrepancy underscores the impact of eye-specific factors. It suggests that the i-wave attenuation may be a manifestation of the biomechanical and functional environment of the affected eye. Specifically, this may reflect a geometric signal dilution where the expansion of the retinal surface area due to axial elongation increases the distance between signal generators and recording electrodes.

Additionally, amblyopia affecting the highly myopic eye may further contribute to the observed i-wave modifications by creating a synergistic deficit where mechanical retinal strain is compounded by the lack of neurotrophic stimulation from a suppressed visual cortex. While existing literature [28] addresses the effects of amblyopia on ERG components related to both outer and inner retinal function, we noted a paucity of reports specifically investigating i-wave integrity in these patients. Consequently, the observed

inner retinal dysfunction may be interpreted through two complementary lenses:

- i. As a consequence of cortical suppression: reduced visual drive in the amblyopic eye may lead to diminished inner retina processing.
- ii. As a primary contributor: structural or functional deficits inherent to high myopia (e.g., axial elongation-induced mechanical alterations) may degrade initial signal integrity, thereby exacerbating the development of amblyopia.

Therefore, comprehensive electrophysiological studies examining i-wave characteristics in both myopic eyes and amblyopic patients are essential to clarify these mechanisms and advance our understanding of retinal involvement in myopia.

#### Strength and limitations

The primary limitation of our study is the small number of included patients; however, given the rarity of unilateral high myopia, recruiting a larger cohort is challenging. Furthermore, the condition is often overlooked because the better visual acuity in the unaffected eye masks reduced vision in the amblyopic fellow eye. The small number of cases limited the possibility of conducting thorough statistical analyses and correlation investigations.

Amblyopia in highly myopic eyes may constitute a confounding factor in our study for two reasons:

1. It may contribute to the observed i-wave modifications through a combined deficit of reduced neurotrophic stimulation from a suppressed visual cortex in addition to the mechanical strain characteristic of highly myopic eyes.
2. Oculomotor instability and unstable fixation, typical of highly myopic amblyopic eyes, may affect the measurements, which should be considered when interpreting the results.

Due to the limitations of the RETeval ERG system in the context of i-wave extraction and the limited existing evidence [29]; our findings should be interpreted with caution, and further validation using conventional ERG systems would be valuable to confirm the robustness of i-wave measurements obtained with RETeval.

A key strength of our study is the novelty of the topic: the i-wave, a minimally explored component of the photopic electroretinogram to date, has been especially understudied in the context of myopia. To our knowledge, this is the first report addressing i-wave characteristics specifically in patients with unilateral high myopia.

Another strength of the study is its intra-individual comparison design between highly myopic and low-myopic/emmetropic fellow eyes of UHM patients, which offer a powerful approach for isolating the retinal mechanisms underlying myopization.

Our findings highlight the potential of the photopic ERG i-wave as a promising biomarker for detecting retinal signaling alterations underlying the development of myopic refractive error.

#### Case significance

The photopic ERG i-wave emerges as a promising biomarker for retinal signaling alterations in myopia development.

**Author contributions** Conception and design: Mirella T. S. Barboni, Noémi Széll, Anett Porempovics. Acquisition, analysis and interpretation of data: Mirella T. S. Barboni, Anett Porempovics, Sára Makhoul, Noémi Széll. Drafting the work: Anett Porempovics, Mirella T. S. Barboni, Noémi Széll. Review of the work: Mirella T. S. Barboni, Noémi Széll, Mariann Fodor. Final approval of the version to be published: Noémi Széll, Mirella T. S. Barboni, Mariann Fodor.

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**Data availability** No datasets were generated or analysed during the current study.

#### Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethics approval** All procedures were performed in accordance with the Declaration of Helsinki (1964) and its later amendments or comparable ethical standards. The study protocol was approved by the Regional Scientific and Research Ethics Committee (ETT RKEB, registration number: DE RKEB/IKEB 7115–2025).

**Informed consent** Written informed consent was obtained from all participants or their legal guardians for study participation and publication of anonymized clinical data and images.

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