Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
2024, Vol. 44(9) 1–8

DOI: 10.1177/03331024241276501
journals.sagepub.com/home/cep

Sage

Lack of a direct link between macular cones function and photophobia in interictal migraine

Francesco Casillo[1], Antonio Di Renzo[2], Gabriele Sebastianelli[1], Chiara Abagnale[1], Francesco Martelli[3], Cherubino Di Lorenzo[1], Mariano Serrao[1], Benedetto Falsini[4,5], Vincenzo Parisi[2], and Gianluca Coppola[1]

Abstract

Background: It is still debatable whether the mechanisms underlying photophobia are related to altered visual cortex excitability or specific abnormalities of colour-related focal macular retino-thalamic information processing.

Methods: This cross-sectional study examined Ganzfeld blue-red (B-R) and blue-yellow (B-Y) focal macular cone flash ERG (ffERG) and focal-flash visual evoked potentials (ffVEPs) simultaneously in a group of migraine patients with (n = 18) and without (n = 19) aura during the interictal phase, in comparison to a group of healthy volunteers (HVs) (n = 20). We correlate the resulting retinal and cortical electrophysiological responses with subjective discomfort from exposure to bright light verified on a numerical scale.

Results: Compared to HVs, the amplitude and phase of the first and second harmonic of ffERG and ffVEPs were non-significantly different in migraine patients without aura and migraine patients with aura for both the B-R and the B-Y focal stimuli. Pearson's correlation test did not disclose correlations between clinical variables, including the photophobia scale and electrophysiological variables.

Conclusions: These results do not favour interictal functional abnormalities in L-M- and S-cone opponent visual pathways in patients with migraine. They also suggest that the discomfort resulting from exposure to bright light is not related to focal macular retinal-to-visual cortex pathway.

Keywords

aura, colour, ERG, photophobia, retina, VEP

Date received: 28 May 2024; accepted: 27 July 2024

Introduction

Photophobia (i.e. the clinical hypersensitivity to environmental light stimuli) is reported in all forms of migraine and many neuro-ophthalmic disorders (1). It is included as one of the major criteria for migraine in the International Classification of Headache Disorders, 3rd edition (ICHD-3) (2), being present during and even between attacks (3). During the last few years, the mechanisms underlying photophobia have been the subject of intense research scrutiny (1). In some studies, the mechanism reported to be primarily linked to a hyperexcitability of the visual cortex (4–6) and, in others, to a calcitonin gene-related peptide-dependent sensitization mechanism

[1]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino ICOT, Latina, Italy
[2]IRCCS – Fondazione Bietti, Rome, Italy
[3]Department of Cardiovascular and Endocrine-Metabolic Diseases, and Ageing, National Institute of Health, Rome, Italy
[4]Department of Ophthalmology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[5]Ospedale Pediatrico Bambino Gesù IRCCS, Rome, Italy

Corresponding author:
Francesco Casillo, Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome Polo Pontino – ICOT, Via Franco Faggiana 1668 – 04100, Latina, Italy.
Email: francesco.casillo@uniroma1.it

(7) and/or the mediation of an intrinsically photosensitive retinal ganglion cell population (8). The latter are preferentially sensitive to blue light and establish direct connections with the nuclei of the lateral geniculate complex, which receive input from trigeminal and retinal afferents, thus being unique in perceiving light as a nociceptive signal (9). Consistent impaired colour vision-driven in outer retinal layers by cone photoreceptors for the blue-yellow axis (S-cones) or middle and longer wavelength (M- and L-cones) was observed among different psychophysical experimental tasks in migraine (10,11). Moreover, using fast flicker (30 Hz) single-colour electroretinogram (ERG), a reduced ERG and flash visual evoked potentials amplitudes with green light were described in migraine (12). These responses reflect non-opponent, luminance post-receptorial mechanisms, which are highly variable across individuals and presumably reflect the relative numbers of L- and M-cones (13).

By lowering the temporal stimulation frequency ($\leq$ 12 Hz), it is possible to record blue-red (L-M) and blue-yellow (S-(L + M)) cone chromatic opponent isolating focal ERGs from humans (13,14). The resulting ERG responses are more stable and are consistent with their generation by cone-opponent, chromatic mechanisms (15).

The present cross-sectional study examines Ganzfeld blue-red (B-R) and blue-yellow (B-Y) focal macular cone flash ERG (ffERG) and focal-flash visual evoked potentials (ffVEPs) simultaneously in a group of migraine patients with (MA) and without aura (MO) during the interictal phase compared to a group of healthy subjects. We correlate the resulting retinal and cortical electrophysiological responses with subjective discomfort from exposure to bright light verified on a numerical scale.

Methods

Based on the diagnostic criteria of the ICHD-3 (2), 40 consecutive MA and MO patients consulting our headache clinic at the "Sapienza" University of Rome Polo Pontino ICOT (Latina, Italy) who agreed to undergo an electrophysiological study were enrolled. Forty-five patients affected by migraine were recorded. Recordings were performed in the between-migraine-attack phase, defined as patients without headaches for at least three days before and three days after the day of the recording, checked by telephone interview. Five patients were not included in the analysis because they experienced a migraine attack within three days following the recording session. As a result, recordings from forty patients affected by migraine with (n = 20; ICHD code 1.2.1) and without (n = 20; ICHD code 1.1) aura were considered eligible for the analysis. For comparison, we recruited and recorded a group of 20 healthy volunteers (HVs), whose inclusion criteria included no personal or familial history of migraine, no regular medication intake except for the contraceptive pill and no other medical conditions such as neurological or psychiatric illnesses. Participants in the control group were recruited from university students and hospital personnel, ensuring a diverse but demographically comparable sample in the patient cohort.

Patients aged 18–65 years were evaluated for eligibility in this study based on specific criteria. Inclusion criteria include having a history of migraine for at least one year with or without aura and experiencing two to eight migraine attacks per month. Exclusion criteria consist of receiving prophylactic treatment in the past three months, medication overuse, pregnancy or lactation in women, and the presence of systemic, neurological, including neuro-ophthalmological, or psychiatric disorders that could impact the electrophysiological assessment as determined by the investigators. We collected specific data on the patient's clinical features, including the duration of their migraine illness in years, the number and duration of migraine attacks per month, the severity of headaches (measured on a Visual Analogue Scale from 0 to 10) and the days since the last migraine attack (Table 1). Moreover, all patients were asked to answer the two following questions:

1. During your usual migraine attack, how intense, on average, is the discomfort resulting from exposure to bright light? (from 0 to 10, where 0 is no discomfort and 10 is the maximum intensity of discomfort)?

Table 1. Clinical and demographic characteristics of healthy volunteers (HV) and migraine patients without (MO) and with aura (MA) recorded between attacks.

	HV (n = 20)	MO (n = 19)	MA (n = 18)
Women (n)	14	15	14
Age (years)	29.1 ± 7.7	31.0 ± 11.1	32.1 ± 8.2
Duration of migraine history (years)		14.4 ± 9.3	15.6 ± 8.8
Attack frequency/month (n)		2.9 ± 2.2	3.5 ± 3.4
Attack duration (hours)		20.1 ± 22.0	19.6 ± 15.9
Days since the last migraine attack (n)		11.3 ± 13.3	15.0 ± 11.8
Mean severity of usual migraine attack (n)		7.4 ± 1.2	8.0 ± 1.6
Amount of visual discomfort during attacks		6.0 ± 2.0	7.2 ± 2.1
Amount of visual discomfort between attacks		2.9 ± 2.4	3.9 ± 2.8

Data are expressed as the mean ± SD.

2. When you have no headache, how intense, on average, is the amount of discomfort resulting from exposure to bright light? (from 0 to 10, where 0 is no discomfort and 10 is the maximum intensity of discomfort)?

All patients completed a headache diary sent to them upon scheduling a consultation appointment for a minimum of one month prior to their initial visit.

Every participant in the study underwent a comprehensive neuro-ophthalmological assessment, which involved assessing intraocular pressure, best-corrected visual acuity, slit-lamp biomicroscopy and binocular indirect ophthalmoscopy. Women were studied when they were not in their premenstrual or menstrual phases to reduce the impact of hormonal fluctuations. Both patients and controls were observed in the same laboratory at the same time of day. All participants provided written informed consent to take part in the study. The study received approval from the local ethics committee and was carried out in compliance with the Declaration of Helsinki.

ffERG and ffVEP recordings

The electro-functional examinations were recorded using the following set-up. For ffERG, two Ag–AgCl electrodes on the lower eyelids (active on the right and reference on the left) and a ground gold-cup electrode on the forehead; for ffVEP, three electrodes, one on Oz (active), another on the forehead (reference) and a third ground electrode on the right arm. The electrophysiological signals were amplified by D360 pre-amplifiers (Digitimer Welwyn Garden City, UK) (band-pass 0.05–2000 Hz, gain 1000) and sampled at 4000 Hz using a CED power 1401 device (Cambridge Electronic Design Ltd, Cambridge, UK) and band-pass filtered off-line (3–300 Hz) using Signal, version 3.11 (Cambridge Electronic Design Ltd). For each study participant, we acquired 600 repetitions lasting 125 ms at a stimulus frequency of 8 Hz. Single sweeps exceeding a threshold voltage (25 μV) were automatically rejected aiming to minimize artifacts coming from blinks or eye movements. The signals were analysed off-line by applying a discrete Fourier transformation from which we extracted the amplitude (in μV) and phase (in degree) of the first (1F) and second (2F) harmonics of the ffERG and ffVEP (Figure 1).

Visual stimuli

During the same session, ffERG and ffVEP were simultaneously monocularly recorded from the central 18° of the right eye in response to two chromaticity modulation uniform opponent B-R and B-Y field stimuli superimposed on an equiluminant steady-adapting white background with a luminance of 5 cd/m^2

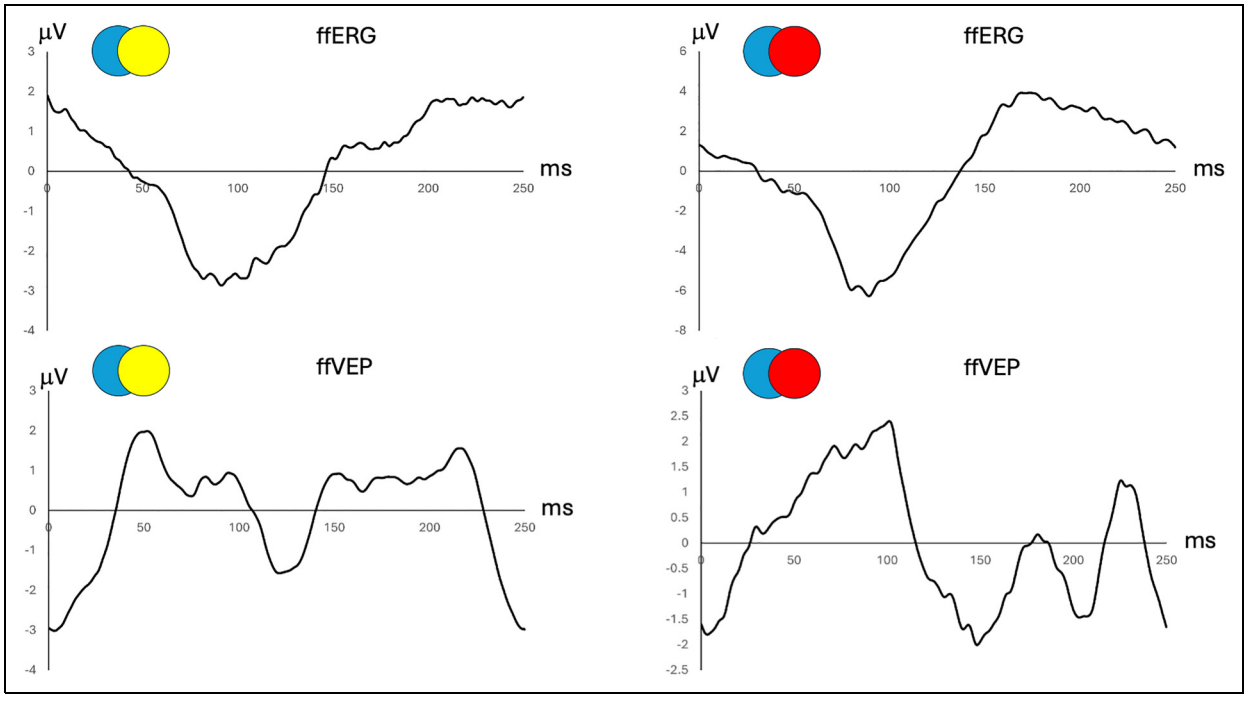

Figure 1. A representative S- (blue-yellow, left) and M-L- (blue-red, right) cone-driven focal-flash ERG (upper) and focal-flash visual evoked potentials (VEP) (lower) waveforms recorded from one healthy volunteer. The simultaneous recording of ffERG and ffVEP were obtained in response to the two-chromaticity modulation uniform opponent 8 Hz flickering colour field stimuli superimposed on an equiluminant steady-adapting white background with luminance of 5 cd/m^2. The colour ratio for the blue-yellow stimulation was defined as $Y/(Y+B) = 0.72$, with Michelson contrasts of 0.54, 0.80, and 1 for L-, M- and S-cone families, respectively. The colour ratio for the blue-red stimulation was $B/(R+B) = 0.44$, with Michelson contrasts of 0.17, 0.82 and 1 for L-, M- and S-cone families, respectively.

to minimize stray light. The flickering frequency was kept at 8 Hz aiming to maximize evoked potentials. Subjects underwent a preadaptation period of 10 minutes to the background illuminance and fixated monocularly at a 0.25° central fixation mark under the constant monitoring of an external observer.

Stimuli were generated by three independently controlled ultrabright red, green and blue LED arrays (peak wavelengths respectively at 620, 530 and 465 nm) presented on the rear of a Ganzfeld bowl. A diffusing filter in front of the LED array made it appear as a uniform stimulus field. The stimuli were controlled by a custom-made software, which could independently control the mean luminance, contrast, phase and waveform of a light stimulus generated by each LED array. For this experimental setup, the diodes driver currents were square-wave modulated, 180° out of phase (blue in counter-phase with red or yellow) between zero and a maximum luminance (15.8, 16.7 and 6.9 cd/m^2, respectively, for red, green and blue arrays). International Commission on Illumination (CIE) coordinates were ($x = 0.68$; $y = 0.32$) for the red LED, ($x = 0.24$; $y = 0.71$) for the green LED and ($x = 0.13$;$y = 0.64$) for the blue LED.

The excitation of each cone type was estimated by multiplying each LED emission spectrum with the psychophysically based cone fundamentals based on the Stiles & Burch 10° colour-matching functions (16) and integrating over the wavelength range (17).

For the B-R field stimuli colour ratio, defined as $r = B/(R + B)$, was 0.44. Michelson contrasts for L-, M- and S-cone families were 0.17, 0.82 and 1, respectively.

The B-Y field colour ratio, defined as $r = Y/(Y + B)$, was 0.72. Michelson contrasts for the L-, M- and S-cone families were 0.54 0.80, and 1, respectively.

Data processing

Time-domain ffERG and ffVEP data were collected and decomposed per group into 1F and 2F Fourier components. Each participant's and component's amplitude and phase were determined, and the mean amplitudes and phases of the groups were acquired by descriptive statistics (Tables 2 and 3).

Sample size calculations were based on a preliminary sample of participants (five for each group). We used the ffERG second harmonic component by B-R visual stimulation to compute the sample size. With 5% alpha error and 20% of beta error (power = 80%), we obtained 19 participants for HV (mean = 0.76 μV, phase = 0.51 rad; variance = 0.39) and MO (mean = 0.43 μV, phase = −0.51 rad; variance = 0.08) patient groups. Moreover, we obtained 18 participants for HV (mean = 0.76 μV, phase = 0.51 rad; variance = 0.39) and MA (mean = 0.45 μV, phase = −0.53 rad; variance = 0.09) patient groups.

Using T2circ, inferential statistics were carried out to compare the ffVEP and ffERG first and second harmonics of healthy controls and MO patients (18).

T2circ is related to an F distribution with 2 and 2M1 + 2M2 − 4 degrees of freedom, where M1 and M2 are the number of participants for each group.

Spearman's correlation coefficient was used to search for correlations between clinical, discrete variables (migraine attacks/month, mean severity of headache/month (0–10), days since the last migraine attack and photophobia scale between and during the attacks (0–10)) and electrophysiological data.

$p < 0.05$ was considered statistically significant.

Results

Assessable ffERG and ffVEPs were obtained from 37 study participants, none of whom felt discomfort during the recording session. Three recordings were not included in the analysis because of their poor quality.

For B-R focal stimuli, we did not find significant between groups differences in amplitude and phase both for ffERG

Table 2. Blue-yellow opponent macular focal-flash electroretinogram (ffERG) and focal-flash visual evoked potentials (ffVEP).

	HV (N = 20)	MO (N = 19)	MA (N = 18)
ffERG			
First harmonic			
Grand-average amplitude (μV)	1.71	1.40	1.08
Grand average phase in degrees	71°.37	69°.84	47°.78
Second harmonic			
Grand-average amplitude (μV)	0.45	0.51	0.62
Grand average phase in degrees	−78°.70	−37°.11	−58°.32
ffVEP			
First harmonic			
Grand-average amplitude (μV)	0.52	0.55	0.55
Grand average phase in degrees	−52°.97	−41°.36	89°.65
Second harmonic			
Grand-average amplitude (μV)	1.14	1.11	1.04
Grand average phase in degrees	14°.35	28°.81	30°.19

HV = healthy volunteer; MO = migraine patients without aura; MA = migraine patients with aura.

Table 3. Blue-red opponent macular focal-flash electroretinogram (ffERG) and focal-flash visual evoked potentials (ffVEP).

	HV (N = 20)	MO (N = 19)	MA (N = 18)
ffERG			
First harmonic			
Grand-average amplitude (μV)	2.02	2.16	1.89
Grand average phase in degrees	61°.28	50°.60	56°.29
Second harmonic			
Grand-average amplitude (μV)	1.26	1.06	1.13
Grand average phase in degrees	80°.58	−71°.77	−83°.27
ffVEP			
First harmonic			
Grand-average amplitude (μV)	0.64	0.18	0.64
Grand average phase in degrees	−78°.70	62°.26	−83°.85
Second harmonic			
Grand-average amplitude (μV)	1.13	0.83	0.98
Grand average phase in degrees	16°.40	12°.84	28°.14

HV = healthy volunteer; MO = migraine patients without aura; MA = migraine patients with aura.

(HV vs. MO first harmonic, $F = 0.16$, $p = 0.85$, and second harmonic, $F = 1.63$, $p = 0.20$; HV vs. MA first harmonic, $F = 0.06$, $p = 0.94$, and second harmonic $F = 0.68$, $p = 0.51$) and ffVEPs (HV vs. MO first harmonic, $F = 0.92$, $p = 0.40$, and second harmonic, $F = 0.58$, $p = 0.56$; HV vs. MA first harmonic, $F = 0.01$, $p = 0.99$, and second harmonic, $F = 0.35$, $p = 0.70$).

Similarly, we did not find significant between groups differences for B-Y focal stimuli in amplitude and phase both for ffERG (HV vs. MO first harmonic, $F = 0.75$, $p = 0.29$, and second harmonic, $F = 1.43$, $p = 0.25$; HV vs. MA first harmonic, $F = 2.04$, $p = 0.14$, and second harmonic, $F = 0.59$, $p = 0.56$) and ffVEPs (HV vs. MO first harmonic, $F = 0.10$, $p = 0.90$, and second harmonic, $F = 0.43$, $p = 0.65$; HV vs. MA first harmonic, $F = 1.33$, $p = 0.27$, and second harmonic, $F = 0.81$, $p = 0.45$) (Figure 2).

Pearson's correlation test did not disclose correlations between clinical variables, including the photophobia scale and electrophysiological variables. Importantly, in our sample, we did not find any significant relationship between the time since the last migraine attack and electrophysiological parameters or visual discomfort scale scores.

Discussion

Our study indicates no significant interictal abnormalities in L-, M- and S-cone visual pathways in migraine patients. The lack of correlation between photophobia and electrophysiological measures suggests that light discomfort is not related to these pathways.

The ERG is a retinal potential response generated by the absorption of photons in photopigments, including several post-receptorial processes and cells such as bipolar cells, retinal ganglion cells and amacrine cells (15,19). ERG signals can be utilized to investigate cone-driven responses by manipulating L- (long wavelength sensitive), M- (middle wavelength sensitive) and S- (short wavelength sensitive) cones simultaneously with varying proportions. The responses obtained indicate the involvement of the parvocellular pathway with L-, M- and S-cone opponency (15,20). The macular focal cone ERG is a sensitive test used to identify, classify and monitor the advancement of central retinal dysfunction in various neuroophthalmological conditions (21). The ERG signal has been suggested to reflect certain features of cone opponent processes and may therefore be associated with colour vision. In the present study, we utilized two distinct colour opponent stimuli to modulate at the 20° eccentricity macular area: a B-R stimulus and a B-Y stimulus. The former targeted the M-L-cones visual pathway, whereas the latter targeted the S-cones system. We chose the B-R stimulus instead of the red-green one because of the difficulty of distinguishing responses induced by the overlapping absorption spectra of the L- and M-cones. Adapting one cone will unavoidably affect the other (21). The results of our study suggest that both the L-M- and S-cone opponent visual pathways are normal in migraine between attacks.

Recording full-field (Ganzfeld) ERG in response to single-flash and 30 Hz flickering flashes of coloured light in migraine patients, Noseda et al. (12) found a significantly smaller light-adapted single-flash cone ERG b-wave amplitude in response to green light than that elicited by blue and white, but a larger blue b-wave amplitude compared to all other colours. They also observed significantly smaller b-wave light flicker cone ERG amplitudes elicited by green light than those elicited by blue, red and white light. Based on these results, they argued that activation of cone-mediated retinal pathways can play a role in the photophobic effects of colours. These results differ from ours and are difficult to compare with our data and may be related to the differences in patients' selection criteria and/or stimulus protocol. In the study by Noseda et al. (12), there was no direct comparison with healthy controls, so we do not know whether their data fall within the range of

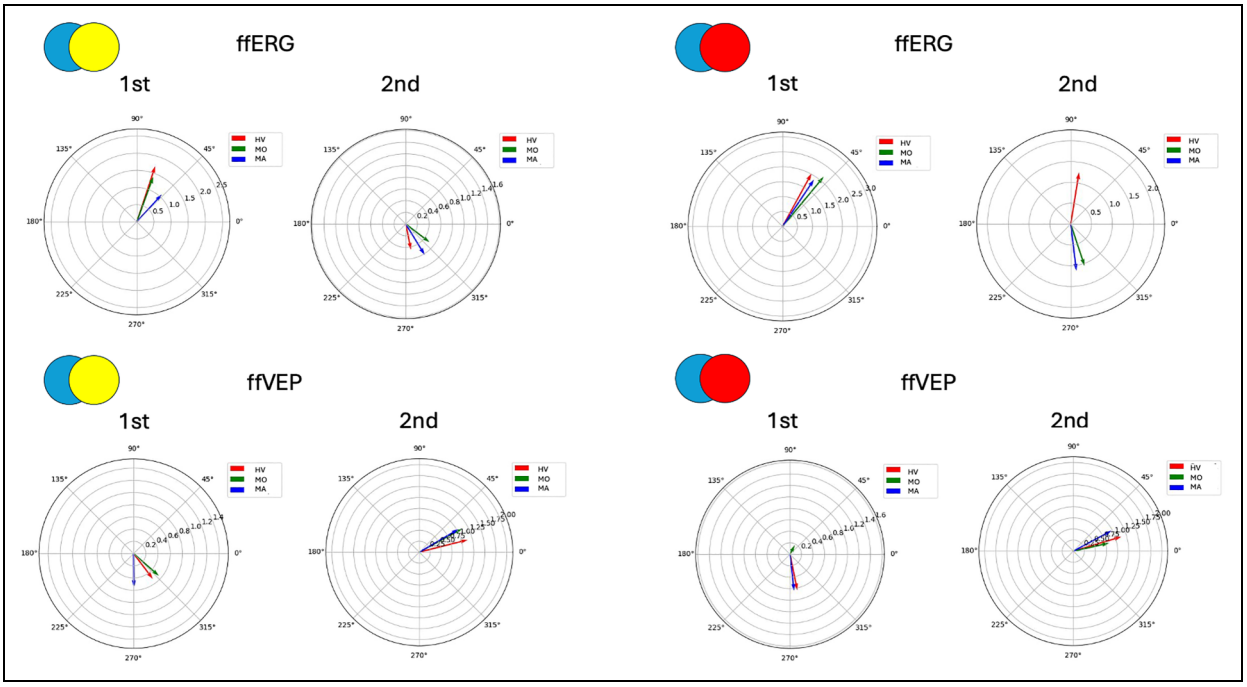

Figure 2. The constituent component vectors (amplitude and phase) for the first and second harmonic component for S- (blue-yellow, left) and M-L- (blue-red, right) cone-driven focal-flash ERG (upper) and focal-flash visual evoked potentials (VEP) (lower).

normality. Flashes at 30 Hz, overlaid on a background that adapts to light, are mainly produced by cone-on and off-bipolar cells that produce the ERG. This process relies on the activity of L- and M-wavelength-sensitive cones, with minimal involvement of S-wavelength-sensitive cones because of their reduced temporal resolution (22). Additionally, they used a full-field non-colour-opponent single-flash colour stimulus, which contrasts with our macular focal colour-opponent B-R and B-Y visual stimuli. Finally, Noseda et al. (12) mixed together patients with and without aura, episodic and chronic, without clarifying during which phase of the migraine cycle patients were recorded and did not in any way directly correlate patients subjective perceptions of light discomfort with ERG responses. In a further study from the same research group, full-field (Ganzfeld) single-flash and 30 Hz flickering flashes and flash VEPs obtained from a group of migraine patients were compared against a group of healthy controls (23). They found no significant differences in cone ERG waves and VEP amplitudes between the migraine patients and healthy controls in any of the examined colours of light, whereas rod single-flash ERG b-wave amplitude was greater in migraine patients in response to all colours except blue. Based on the latter results, they concluded that hypersensitivity to light among migraine patients may originate in the retinal rods rather than retinal cones or the visual cortex, despite the fact that, as in the previous study, they did not specify the migraine phase in which patients were recorded and did not check for a correlation between rod ERG responses and subjective assessments of visual discomfort in response to light (23).

Cortical hypersensitivity to light has been implicated in migraine photophobia. Using H_2O^{15} positron-emitting tomography, Boulloche et al. (6) showed a luminance-intensity-dependently stronger visual cortical activation in interictal migraine patients than in controls. Patients with episodic migraine and interictal photosensitivity exhibit increased cortical thickness in specific brain regions (the right parietaloccipital and left fronto-parietal), indicating a connection between persistent light sensitivity and structural changes (5). However, in these studies, the researchers did not verify if cortical metabolism and thickness change according to the subjective level of visual discomfort or, in other words, if they were directly related to photophobia (5,6). The interictal visual discomfort score and the ictal migraine photophobia score were higher than controls in both MO and MA in one study, but only in MA patients were these scores positively correlated with BOLD activation in the visual cortex (4), suggesting underlying differences between groups. Although a direct comparison with our data is not possible as a result of the intrinsic methodological differences, we did not confirm a direct relationship between the subjective perception of light discomfort and colour-opponent cortical flash VEP parameters or any other migraine clinical feature in our MA patients. Considering the relative differences in the electrophysiological techniques and stimulus parameters, our colour-opponent cortical flash VEP results are in line with the previous one, which also showed no significant differences between migraine patients and healthy controls (12,23) and may suggest that discomfort resulting from exposure to bright light is not related to visual cortex. In support of this observation, bright lights in rodents enhance

trigeminal reflex blink amplitude and spontaneous blinking rate, even after optic nerve lesioning, bypassing the central visual system (24). However, based on previous evidence, we cannot exclude a visual cortical involvement secondary to a primary thalamic (8) and/or trigeminal nucleus (9) activation.

A significant limitation of the present study is that we only relied on self-reported photosensitivity to quantify light-induced visual discomfort. It is unclear whetherthose who reported photosensitivity also had aberrant visual discomfort thresholds as determined through objective testing. Macular focal cone ERG cannot capture the intricate spatial details that can be detected by multifocal ERG and microperimetry. Furthermore, as a limitation, we acknowledge not having performed an additional recording using white light stimulation, as in Noseda et al. (12). However, our research focused on chromatic stimuli to specifically investigate the cone-opponent pathways that are relevant to migraine-related photophobia. Finally, as a possible study limitationm we recognize that, for recordings of ffERG, active and reference electrodes were made of Ag-AgCl material, whereas those of the ground were made of gold, implying different electrical properties.

Conclusions

The selective combined recordings of retinal macular foveal focal-flash ERG and cortical focal-flash VEP after B-R and B-Y visual stimulations did not disclose significant differences between MO and MA patients between the attacks compared to healthy controls. Future studies should be devoted to verifying the integrity of other cellular subpopulations of the retina, especially those located in the paramacular region related to the magnocellular stream, such as associational ganglion cells, which are more closely interconnected with retinal trigeminal nociceptors (24).

Clinical implications

- During the interictal period, there were no significant differences in ffERG and ffVEP responses between migraine patients and healthy controls.
- Additionally, there were no significant correlations between electrophysiological variables and the light-induced visual discomfort.
- Our results suggest that colour-related macular retinal function does not contribute to photophobia in interictal migraine.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical statement

All participants provided their written informed consent to take part in the study. The study received approval from the local ethics committee and was carried out in compliance with the Declaration of Helsinki.

Funding

The contribution of the G. B. Bietti Foundation to this paper was supported by the Italian Ministry of Health and Fondazione Roma.

ORCID iDs

Francesco Casillo https://orcid.org/0000-0003-4642-950X
Gabriele Sebastianelli https://orcid.org/0000-0002-4231-4417
Gianluca Coppola https://orcid.org/0000-0002-8510-6925

References

1. Digre KB and Brennan KC. Shedding light on photophobia. *J Neuroophthalmol* 2012; 32: 68–81.
2. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; 38: 1–211.
3. Main A, Dowson A and Gross M. Photophobia and phonophobia in migraineurs between attacks. *Headache* 1997; 37: 492–495.
4. Cucchiara B, Datta R, Aguirre GK, et al. Measurement of visual sensitivity in migraine: validation of two scales and correlation with visual cortex activation. *Cephalalgia* 2015; 35: 585–592.
5. Chong CD, Starling AJ and Schwedt TJ. Interictal photosensitivity associates with altered brain structure in patients with episodic migraine. *Cephalalgia* 2016; 36: 526–533.
6. Boulloche N, Denuelle M, Payoux P, et al. Photophobia in migraine: an interictal PET study of cortical hyperexcitability and its modulation by pain. *J Neurol Neurosurg Psychiatry* 2010; 81: 978–984.
7. Mason BN, Kaiser EA, Kuburas A, et al. Induction of migraine-like photophobic behavior in mice by both peripheral and central CGRP mechanisms. *J Neurosci* 2017; 37: 204–216.
8. Noseda R, Kainz V, Jakubowski M, et al. A neural mechanism for exacerbation of headache by light. *Nat Neurosci* 2010; 13: 239–245.
9. Okamoto K, Tashiro A, Chang Z, et al. Bright light activates a trigeminal nociceptive pathway. *Pain* 2010; 149: 235–242.
10. Shepherd AJ. Colour vision in migraine: selective deficits for S-cone discriminations. *Cephalalgia* 2005; 25: 412–423.

11. Main A, Vlachonikolis I and Dowson A. The wavelength of light causing photophobia in migraine and tension-type headache between attacks. *Headache* 2000; 40: 194–199.
12. Noseda R, Bernstein CA, Nir RR, et al. Migraine photophobia originating in cone-driven retinal pathways. *Brain* 2016; 139: 1971–1986.
13. Challa NK, McKeefry D, Parry NRA, et al. L- and M-cone input to 12Hz and 30Hz flicker ERGs across the human retina. *Ophthalmic Physiol Opt* 2010; 30: 503–510.
14. Aher AJ, McKeefry DJ, Parry NRA, et al. Rod- versus cone-driven ERGs at different stimulus sizes in normal subjects and retinitis pigmentosa patients. *Doc Ophthalmol* 2018; 136: 27–43.
15. Kremers J and Link B. Electroretinographic responses that may reflect activity of parvo- and magnocellular post-receptoral visual pathways. *J Vis* 2008; 8: 11–11.
16. Stiles WS and Burch JM. N.P.L. Colour-matching investigation: final report (1958). *Opt Acta Int J Opt* 1959; 6: 1–26.
17. Stockman A and Sharpe LT. The spectral sensitivities of the middle- and long-wavelength-sensitive cones derived from measurements in observers of known genotype. *Vision Res* 2000; 40: 1711–1737.
18. Victor JD and Mast J. A new statistic for steady-state evoked potentials. *Electroencephalogr Clin Neurophysiol* 1991; 78: 378–388.
19. Viswanathan S, Frishman LJ and Robson JG. Inner-retinal contributions to the photopic sinusoidal flicker electroretinogram of macaques. Macaque photopic sinusoidal flicker ERG. *Doc Ophthalmol* 2002; 105: 223–242.
20. Kremers J and Meierkord S. Rod–cone-interactions in deuteranopic observers: models and dynamics. *Vision Res* 1999; 39: 3372–3385.
21. Kremers J. The assessment of L- and M-cone specific electroretinographical signals in the normal and abnormal human retina. *Prog Retin Eye Res* 2003; 22: 579–605.
22. Robson AG, Frishman LJ, Grigg J, et al. ISCEV Standard for full-field clinical electroretinography (2022 update). *Doc Ophthalmol* 2022; 144: 165–177.
23. Bernstein CA, Nir R-R, Noseda R, et al. The migraine eye. *Pain* 2019; 160: 569–578.
24. Dolgonos S, Ayyala H and Evinger C. Light-induced trigeminal sensitization without central visual pathways: another mechanism for photophobia. *Invest Ophthalmol Vis Sci* 2011; 52: 7852–7858.