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Photophobia in migraine: Electrophysiological analysis of chromatic opponent responses via electroretinogram and visual evoked potential

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Abstract

Background: Migraine is characterized by recurrent headaches and sensory hypersensitivities, with photophobia affecting up to 90% of patients during attacks. The mechanisms underlying ictal photophobia remain unclear, potentially involving altered excitability of the visual cortex, trigeminovascular sensitization, or cone-driven retinal pathways. Prior interictal studies have shown preserved macular cone opponent mechanisms, but ictal investigations are lacking.

Methods: In this prospective study, we simultaneously recorded Ganzfeld blue-red (B-R) and blue-yellow (B-Y) focal flash (8 Hz) macular cone electroretinogram (ERG) and the subsequent visual evoked potential (VEP) in 11 patients with migraine without aura during acute attacks and in 20 healthy volunteers. First (1F) and second (2F) harmonic amplitudes and phases were analyzed using discrete Fourier transformation and T^2circ statistics. Responses were correlated with clinical variables, including photophobia severity (0–10 scale) during attacks, using Spearman's coefficient.

Results: For B-Y stimuli, a selective reduction in ERG 1F amplitude was noted in patients ($F = 4.19$, $p = 0.02$), with preserved phases and no differences in other harmonics or VEP responses. A significant negative correlation was observed between the phase of the first harmonic of the VEP and the level of photophobia during the attack. No significant differences were observed in 1F or 2F ERG/VEP amplitudes or phases for B-R stimuli between patients with migraine and HVs.

Conclusions: Ictal macular cone-opponent pathways remain largely intact in migraine, with a specific S-cone amplitude attenuation suggesting an autonomic-mediated inference on blue-light hypersensitivity. The finding of a correlation of B-Y VEP phase with photophobia implies that this symptom may arise from subcortico-cortical integrations (e.g., thalamic-trigemino-cortical convergence) rather than focal retinal dysfunction.

Keywords

colour, retina, ERG, VEP, blue-light, photophobia

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Background

Migraine manifests as recurrent episodes of moderate to severe headache, often unilateral and pulsating, lasting 4–72 h, and is frequently accompanied by associated symptoms such as nausea, vomiting, and sensory hypersensitivities.[1] Among these, photophobia emerges as a cardinal feature, reported in up to 80–90% of patients with migraine during attacks, serving as a diagnostic criterion, and persisting interictally in 40–60% of cases.[2] Photophobia intensifies headache severity and can exacerbate migraine-related disability by limiting daily activities, such as exposure to screens, outdoor environments, or artificial lighting, often necessitating isolation in darkened rooms and contributing to acute attack prolongation. Despite its prevalence and impact, the mechanisms underlying photophobia in migraine remain intricate and incompletely understood. Proposed mechanisms include hyperexcitability of the visual cortex, calcitonin gene-related peptide (CGRP)-mediated sensitization of trigeminovascular pathways, and direct involvement of intrinsically photosensitive retinal ganglion cells (ipRGCs).[3–5] Supporting this, animal models demonstrate that blue light activates dural nociceptors via ipRGCs-thalamic pathways, mimicking migraine-like photophobia, while CGRP antagonists mitigate these effects.[6,7] Clinically, patients with migraine exhibit wavelength-specific aversion, with blue and red light eliciting greater discomfort than green light, as evidenced by behavioral and psychophysical studies. The aversion persists only to blue light in retinal-blind patients with migraine.[8,9]

Using single-flash cone electroretinography, investigators have reported that green light activates cone-driven retinal pathways less than blue, amber, or red light interictally, suggesting differential involvement of luminance and opponent pathways. However these findings lacked direct comparisons with controls or correlations with photophobia.[8] A recent interictal study employing Ganzfeld blue-red and blue-yellow focal-flash macular cone electroretinogram (ERG) and visual evoked potential (VEP) found no significant differences in amplitudes or phases between patients with migraine and healthy volunteers, nor any associations with clinical variables such as photophobia scales, arguing against abnormalities in these pathways between attacks.[10] However, these findings may not apply to the ictal phase, leaving a knowledge gap, as ictal-specific alterations might explain the phase-dependent severity of photophobia and inform targeted therapies, such as wavelength-filtering lenses[11,12] or pharmacological therapies. To bridge this gap, the present prospective study recorded Ganzfeld blue-red and blue-yellow focal flash macular cone ERG and VEP simultaneously in patients with migraine during an acute attack and compared them with those of healthy volunteers. Responses were additionally correlated with subjective light discomfort on numerical scales during the attack to investigate potential associations between ictal electrophysiological parameters and photophobia severity. Given that photophobia is a prominent symptom during a migraine attack, we hypothesised that photophobia might be related to a specific dysfunction of the cone-driven retinocortical pathways.

Material and methods

Participants

A cohort of 31 individuals was recruited from the headache clinic at the Sapienza University of Rome Polo Pontino ICOT (Latina, Italy). This group consisted of 20 healthy volunteers (HVs) and 11 patients with migraine without aura (MwoA), according to the diagnostic criteria of the International Classification of Headache Disorders (3rd edition). In this study, we only included patients who had a spontaneous migraine attack on the day of the recording session. Recordings were performed within the initial 6 h of their typical pain associated with migraine attack. This study is reported in accordance with the STROBE guidelines for a prospective study.

The HVs group was selected based on criteria excluding any personal or familial history of migraine, regular medication use (except oral contraceptives), and the absence of neurological or psychiatric conditions. Patients were included if they had a confirmed episodic migraine without aura diagnosis for at least one year.[1] Eligibility for patients required an age range of 18 to 65 years, with exclusion criteria encompassing migraine prophylactic treatment within the prior three months, medication overuse, pregnancy or lactation in females, and any systemic, neurological, or psychiatric disorders that might interfere with electrophysiological measurements, as assessed by the research team. No patient had taken any acute treatment prior to electrophysiological recording. All participants underwent a thorough neuro-ophthalmological examination, which included assessment of intraocular pressure, best-corrected visual acuity, slit-lamp biomicroscopy, and binocular indirect ophthalmoscopy. Female participants were evaluated outside their premenstrual or menstrual phases to mitigate hormonal effects. Examinations were conducted in a controlled laboratory environment at a consistent time of day for both groups. Clinical data collected included the duration of migraine history in years, migraine days and duration of attacks per month, headache severity rated on a Visual Analog Scale (VAS) from 0 to 10, and the time elapsed since the last attack. Moreover, to collect photophobia-related data, all patients were asked to answer the following question:

During your migraine attack how intense 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);

Clinical and demographic characteristics of HVs and patients with MowA, recorded during attacks, are shown in Table 1.

Table 1. Clinical and demographic characteristics of healthy volunteers and patients with migraine recorded during attacks. Data expressed as mean ± SD. Headache severity and photophobia refer to the specific attack at the time of recording.

Characteristic	Healthy volunteers	Patients
N	20	11
Females – n	14	7
Males – n	6	4
Age – mean (SD)	28.1 ± 7.7	27.6 ± 10.1
Migraine history – mean years (SD)	—	11.2 ± 7.7
Migraine days – mean n/month (SD)	—	6.5 ± 5.2
Attack duration – mean hours (SD)	—	26.4 ± 25.9
Time from onset to recording	—	4.6 ± 0.8
Pulsating – n (%)	—	8 (72.7%)
Nausea – n (%)	—	10 (90.9%)
Photophobia – n (%)	—	11 (100%)
Phonophobia – n (%)	—	10 (90.9%)
Ictal headache severity – mean (SD)	—	8.3 ± 1.0
Ictal photophobia – mean (SD)	—	7.4 ± 1.5

Written informed consent was obtained from all participants, and the study protocol was approved by the local ethics committee, in accordance with the principles of the Declaration of Helsinki.

Focal flash stimulation protocol

In a single session, for each participant, 600 stimulus repetitions of simultaneous focal flash electroretinography and focal flash VEP recordings were collected, each spanning 125 ms, at a stimulation rate of 8 Hz.

Visual stimulation was performed using:

- Light stimulation restricted to the central 18° macular field, isolating cone-driven opponent mechanisms (L-M and S-cones) critical for color vision.[13]
- Flash modality (8 Hz square-wave modulation) eliciting robust, reproducible responses without requiring pattern reversal, which may be confounded by fixation instability during ictal phases.[14,15]

Participants underwent a 10-min pre-adaptation to the background luminance, followed by monocular fixation on a 0.25° central marker, with fixation monitored continuously by an external observer to ensure compliance. No pharmacological pupil dilation was performed; pupils were in their natural state throughout the recording session, maintained under stable photopic adaptation by the steady equiluminant white adapting background (5 cd/m^2). Visual patterns were produced using three autonomously modulated ultra-bright LED arrays emitting red, green, and blue light (peak wavelengths: 620 nm, 530 nm, and 465 nm, respectively), projected over a rear section of a Ganzfeld dome subtending 18° visual field. LED's spectral output was based on psychophysical cone fundamentals derived from Stiles and Burch's 10-degree color-matching functions, followed by wavelength integration.[16,17] Stimuli consisted of uniform, opponent-chromatic modulations: blue-red and blue-yellow fields, overlaid on a steady, equiluminant white adapting background at 5 cd/m^2 to suppress scattered-light effects.

For blue-red stimuli, the color ratio (r = B/(B + R)) was set at 0.44, yielding Michelson contrasts of 0.17 (L-cones), 0.82 (M-cones), and 1 (S-cones).

For blue-yellow stimuli, the ratio (r = Y/(B + Y)) was 0.72, with contrasts of 0.54 (L-cones), 0.80 (M-cones), and 1 (S-cones).

Cone excitations were calculated using Stiles-Burch 10-degree color-matching functions, integrating LED emission spectra with cone fundamentals to derive Michelson contrasts (e.g., S-cone contrast = 1 for both stimuli, ensuring robust isolation). This approach allows differentiation between parvocellular (color-opponent) and magnocellular (luminance) pathways, potentially revealing anomalies in blue-sensitive response.[18]

Recording setup

The electrophysiological assessment configuration included two silver-silver chloride (Ag-AgCl) electrodes positioned on the inferior eyelids to record signals. A gold-cup electrode was placed on the forehead to serve as a common reference for both ERG and VEP measurements, with an additional electrode at Oz (midline of the occipital region) to capture cortical potentials. The ground electrode was affixed to the right arm to ensure signal stability. This arrangement allowed for simultaneous acquisition of retinal and cortical responses, minimizing interference from extraneous bioelectrical activity.

Data processing

Recorded signals were enhanced using Digitimer D360 preamplifiers, configured with a bandpass filter ranging from 0.05 to 2000 Hz and an amplification factor of 1000. Digitization occurred at a sampling rate of 4000 Hz via a CED Power 1401 interface (Cambridge Electronic Design Ltd, Cambridge, UK). Post-acquisition, signals were offline bandpass-filtered between 3 and 300 Hz using Signal software (version 4.11). To reduce contamination from ocular artifacts such as blinks or saccades, individual epochs surpassing a 25 μV threshold were automatically discarded. Offline analysis involved a discrete Fourier transform to derive the amplitude (expressed in μV) and phase (in degrees) for the fundamental (1F) and second harmonic (2F) components of both focal flash ERG and focal flash VEP waveforms. This approach facilitated precise isolation of frequency-specific responses, enhancing the reliability of data interpretation during acute migraine episodes.

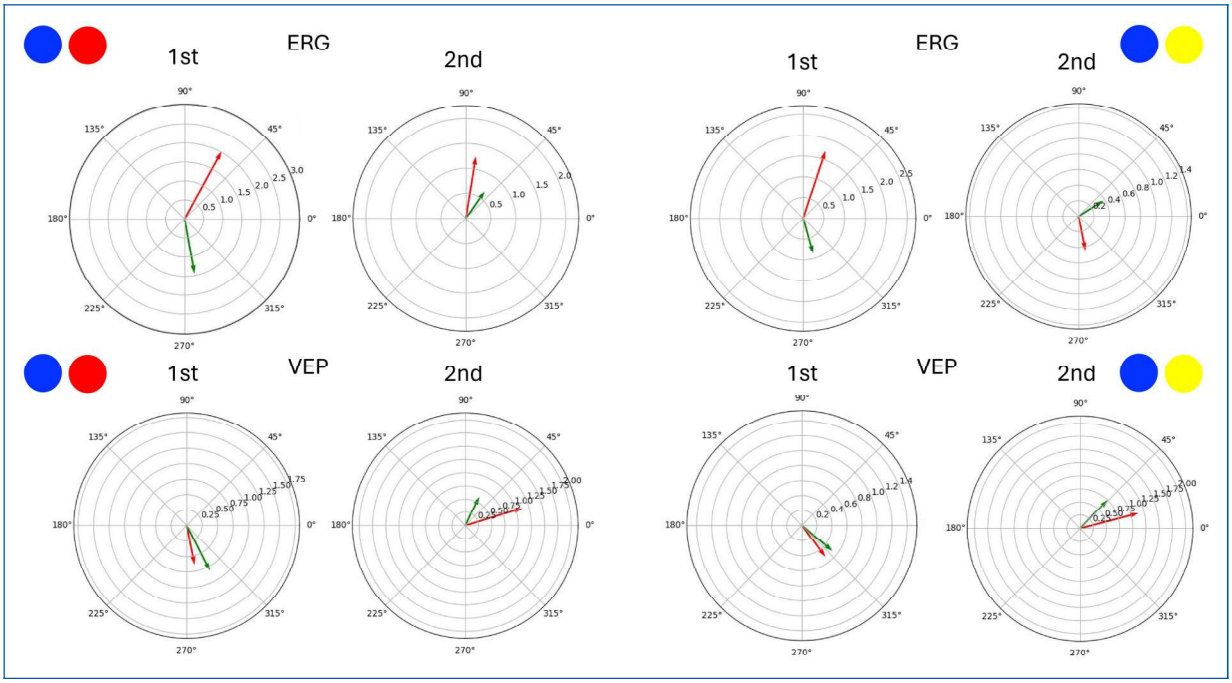


Figure 1. The constituent component vectors (amplitude and phase) for the first and second harmonic component for M-L- (blue-red, left) and S- (blue-yellow, right) and cone-driven focal flash ERG (upper) and focal flash visual evoked potentials (VEP) (lower). The vector for amplitude and phase is coded in red for the healthy volunteers group and in green for the patient group.

Statistical analysis

Group comparisons between the ictal patients with migraine and healthy volunteers were performed using the circular Hotelling T^2 statistic (T^2circ statistic),[19] a specialized inferential tool optimized for vectorial data in steady-state evoked potentials. This analysis was applied independently to the 1F and 2F harmonics of focal flash ERG and focal flash VEP. The T^2circ statistic adheres to an F-distribution with 2 degrees of freedom in the numerator and $2(M_1 + M^2)$ - 4 in the denominator, where M_1 and M^2 represent the sample sizes of the respective groups.

To explore associations between neurophysiological outcomes and clinical manifestations, Spearman's rank correlation coefficient (ρ) was utilized. Correlations were assessed linking focal flash ERG/ focal flash VEP metrics (amplitudes and phases) to key clinical indicators, such as monthly migraine days, average headache intensity on a visual analog scale (VAS; 0–10), and photophobia severity scores (0–10) evaluated during the attack, immediately before recording.

Statistical significance was established at a two-tailed p-value threshold of <0.05, balancing Type I error control with detection of clinically relevant effects in this investigative setting.

Results

Assessable focal flash electroretinogram and focal flash visual evoked potentials recordings were obtained from 31 study participants (20 HVs and 11 MwoA during the ictal phase).

For B-R focal stimuli, no significant between-group (HVs vs. Patients with MwoA) differences were observed in amplitude or phase for focal flash ERG (1F $F = 1.75$, $p = 0.18$; 2F $F = 1.76$, $p = 0.18$) or focal flash VEP (1F $F = 0.18$, $p = 0.84$; 2F $F = 2.39$, $p = 0.10$). Similarly, for B-Y focal stimuli, most comparisons were non-significant for focal flash ERG (2F $F = 1.19$, $p = 0.31$) and focal flash VEP (1F $F = 0.10$, $p = 0.90$; 2F $F = 2.31$, $p = 0.11$). For B-Y, a significant difference emerged in the focal flash ERG 1st harmonic ($F = 4.19$, $p = 0.02$), suggesting potential ictal-specific alterations in S-cone opponent pathways (Figure 1). Spearman's correlation coefficient analysis revealed a significant negative association between the photophobia scale during the attack (0–10) and the phase of the 1F of the focal flash VEP for B-Y stimuli ($\rho = -0.705$, $p = 0.015$, Figure 2).

No other significant associations between clinical variables and electrophysiological parameters for either B-R or B-Y stimuli (all $p > 0.05$) were found.

Discussion

Two key observations emerge from our data collected during migraine attacks:

1. 1F amplitude/phase vector of focal flash ERG for B-Y stimuli, involving the S-cone opponent

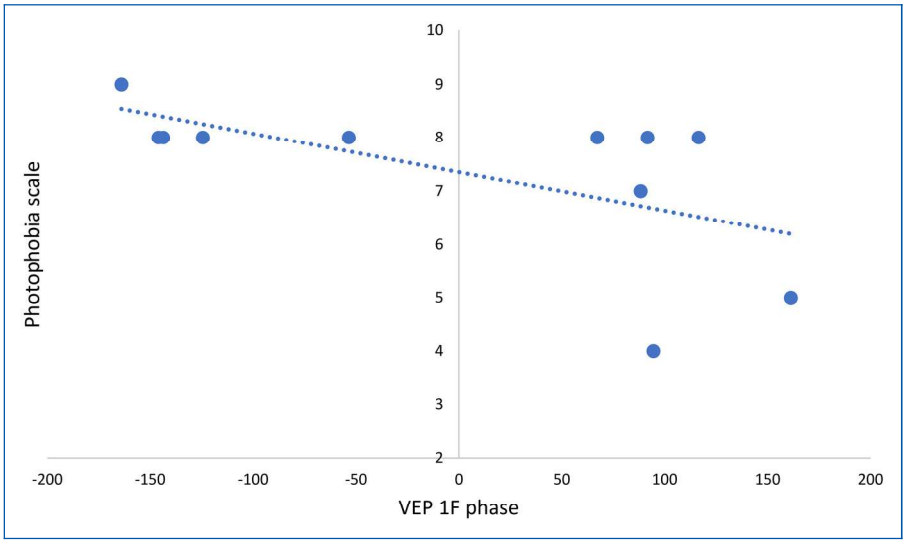


Figure 2. In migraine patients the level of photophobia during the attack correlated negatively with the phase of the first harmonic of visual evoked potentials (VEP 1F).

pathway, showed diminished responses compared to HVs.

2. While no correlation was found between focal flash ERG parameters and photophobia scale, the focal flash VEP parameters, despite being within the normal range, showed a first B-Y harmonic (1F) phase correlation with the severity of photophobia.

The selective amplitude/phase vector changes in B-Y ERG 1F (S-cone pathway) during migraine attacks, compared with HVs, highlight a potential adaptive response unique to the ictal phase that the autonomic nervous system may orchestrate. Noseda et al. have extensively described how photic responses actively engage autonomic circuits. Light, regardless of its wavelength, induced symptom shifts associated with autonomic nervous system activity, such as tearing, excessive salivation, nausea, and a runny nose, as well as those influenced by sympathetic activity, including dry mouth, breathing difficulties, chest pressure, and rapid heartbeats. Overall, the diverse array of autonomic symptoms that lead to the distressing experiences reported by migraine sufferers might be influenced by light-induced stimulation of the retinohypothalamic-parasympathetic (RHP) and retinohypothalamic-sympathetic (RHS) neural pathways.[20] In this framework, the observed attenuation evident in the linear 1F component (reflecting direct stimulus transduction) but not in higher harmonics could represent a transient autonomic suppression of S-cone excitability due to a non-wavelength-selective autonomic suppression of choroidal perfusion. In mammals, the autonomic nervous system plays a pivotal role in regulating ocular blood flow, particularly in the choroid and retina, through a balance of sympathetic and parasympathetic innervation.[21] The sympathetic branch, acting primarily via α-adrenergic receptors on vascular smooth muscles, induces vasoconstriction in choroidal vessels, thereby reducing blood supply to the outer retina, including the photoreceptor layer. In contrast, parasympathetic activity, mediated by cholinergic pathways originating from the pterygopalatine ganglion, promotes vasodilation and enhances choroidal perfusion. This dual innervation ensures precise control over choroidal blood flow, which supplies up to 85% of the oxygen and nutrients required by the outer retina, including the retinal pigment epithelium (RPE) and photoreceptors.[21] From a migraine-related trigeminovascular perspective, the neuroendocrine hypothalamic activation in conjunction with the trigeminovascular system, as seen in neuroimaging studies,[22] may lead to sympathetic overactivation during migraine attacks, exacerbating choroidal vasoconstriction and diminishing the delivery of essential substrates such as oxygen, glucose, and ATP precursors to the RPE and photoreceptors. Short-wavelength-sensitive (S) cones, which are preferentially tuned to blue light (peak sensitivity ~420 nm) and comprise only 5–10% of the total cone population, appear disproportionately vulnerable to these perturbations. This susceptibility arises from their higher expression of oxidative stress markers, greater mitochondrial density, and elevated metabolic demands compared to long-wavelength (L) and medium-wavelength (M) cones. Reduced choroidal flow can induce local hypoxia, impairing phototransduction efficiency and downstream signal amplification in S-cones.[23,24] These regulations align with autonomic manifestations in migraine, which may indirectly influence photoreceptor metabolism, leading to amplitude dampening without phase shifts. Integrating downstream retinal circuitry, this S-cone hypoactivity interfaces with ipRGCs via

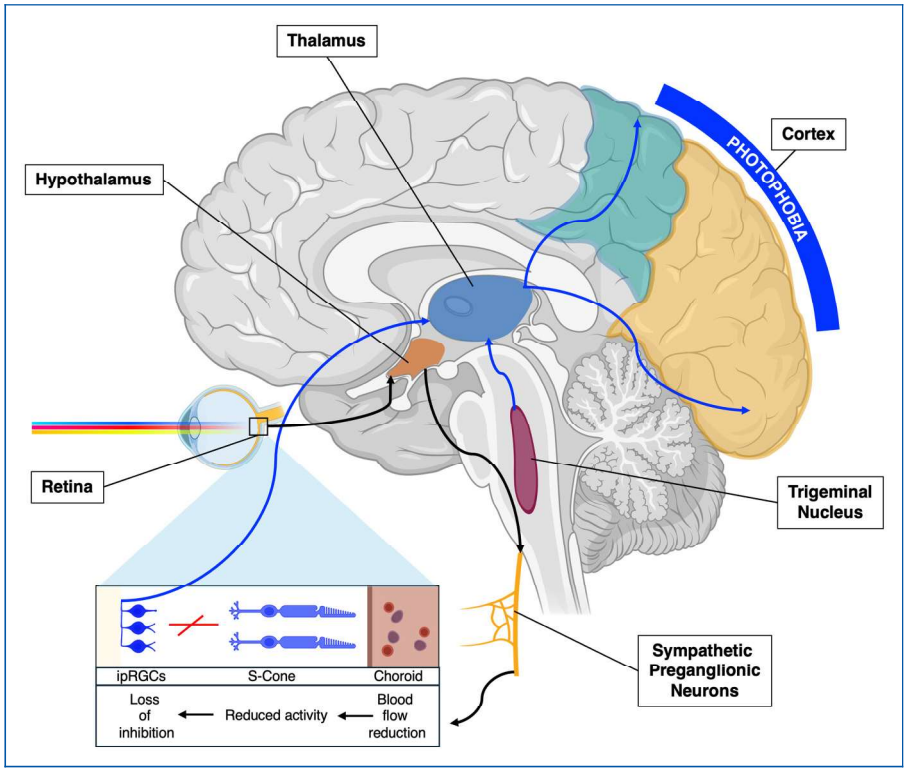


Figure 3. Schematic representation of the proposed pathways underlying ictal photophobia in migraine.
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Light stimulation activates cone photoreceptors in the retina. Two main pathways are illustrated:
[A] the retinothalamocortical pathway (blue arrows): retinal signals are conveyed via retinal ganglion cells, including ipRGCs, to the posterior thalamus, where they converge with ascending trigeminovascular afferents from the trigeminal nucleus. Thalamo-cortical projections subsequently reach visual and somatosensory cortices, where photophobia is ultimately perceived;
[B] the retinohypothalamic-sympathetic pathway (black arrows): non-wavelength-specific retinal signals engage retinohypothalamic sympathetic pathways projecting to sympathetic preganglionic neurons, leading to choroidal vasoconstriction and reduced outer retinal blood flow. This non-wavelength-selective autonomic suppression of choroidal perfusion disproportionately affects S-cones due to their elevated metabolic demands, resulting in reduced S-cone activity (1F B-Y ERG attenuation), loss of inhibitory input to ipRGCs, thereby amplifying the photophobic cascade.

a primate-specific inhibitory pathway. In primates, S-cones excite S-ON bipolar cells, which synapse onto glycinergic amacrine cells that deliver inhibitory input to ipRGCs, yielding a blue-OFF (S-OFF) response.[25] Reduced S-cone activity may diminish this inhibition, leading to ipRGCs disinhibition and heightened melanopsin-driven signals (Figure 3). However, this effect is embedded in a larger cascade: ipRGCs signals project to the posterior thalamus and suprachiasmatic nucleus, interfacing with trigeminovascular nociceptors and hypothalamic autonomic centers.[20] Thus, S-cone hypoactivity acts as a modulator rather than a sole driver of photophobia; its isolated measurement may not capture the cumulative variance in photophobia, leading to non-significant correlations (as in our Spearman analysis, where most p-values >0.05). This interpretation is consistent with animal studies showing light-induced trigeminal sensitization is modulated by the disinhibition of pathways that regulate the sympathetic nervous activity.[26] Clinically, this could account for the wavelength-specific aversion in migraine, where blue light preferentially exacerbates symptoms, prompting therapeutic strategies like blue-filtering lenses[11] or autonomic-targeted agents to restore balance.

The absence of significant correlations between electrophysiological parameters (1F and 2F harmonics) of focal flash ERG for B-R or B-Y stimuli and photophobia severity (assessed via a 0–10 numerical scale) indicates that the macular cone-opponent pathways are not primary drivers of photophobia, even during the headache phase when photophobia is most pronounced. In interictal studies, similar null correlations have been reported, with preserved L-M and S-cone responses failing to align with self-reported light discomfort, suggesting that photophobia originates from mechanisms beyond the retinal photoreceptor function.[10] Clinically, this decoupling between subjective

perception of light discomfort and focal cone retinal activity as assessed with focal flash ERG explains why patients with migraine experience exacerbated headache from ambient light despite normal visual acuity.[3,27] The additional novel finding of a negative correlation between the 1F B-Y focal flash VEP phase and photophobia severity scale despite finding no evidence for atypical focal flash VEP amplitude and phase in our patients, suggests that ictal aversion to light potentially relying on subcortical-cortical integration sites, such as the posterior thalamus, and on ipRGCs projections converging with trigeminovascular afferents to modulate pain and/or on primary visual cortex. In steady-state focal visual evoked potentials, phase measures the temporal offset between the stimulus and the neural response, effectively representing the latency or time lag in the visual pathway.[28] Other electrophysiological evidence observed a negative correlation between subjective levels of photophobia and the amplitude of the driving effect of the electroencephalographic signal to intermittent photic stimulation,[29] as well as with post-movement beta event-related synchronisation, a measure of post-activation excitability in the sensorimotor cortices.[30] Unbalance between inhibitory/excitatory subcortico-cortical mechanisms may underly the so called central sensitization process that is a key pathophysiological mechanism in migraine. It involves heightened neuronal responsiveness within nociceptive and sensory pathways, including those processing visual inputs.[31] Such amplification can disrupt normal temporal dynamics: overactivated neurons may exhibit abnormal synaptic transmission due to altered ion channel kinetics, increased inhibitory feedback to prevent overload, or enhanced integration of convergent trigeminovascular inputs, which introduce processing inefficiencies. In support of this interpretation, some authors have found interictal evidence favouring a relationship between intense visual stimulation and visual discomfort with the functional and metabolic activity of the visual[32] and sensorimotor[4] cortices, the subcortical function of the ventroposteromedial thalamus, and the trigeminal brainstem system.[33] One of the proposed links between the subcortical and cortical dynamics as a source of clinical manifestations in migraine is the so-called thalamocortical dysrhythmia,[34] since a deficient thalamo-cortical drive results in a dysfunction of both inhibitory and excitatory cortical neurons. Evidence favouring abnormal thalamo-cortical network activity also comes from a study of diffusion tensor imaging and resting state functional magnetic resonance imaging techniques during migraine attacks.[35] The negative correlation between the first harmonic of the B-Y phase at the cortical level and self-reported photophobia may reflect a partially sensitized state in which visual signals are not potentiated but are temporally distorted, contributing to an exacerbated perception of photophobia. These findings have therapeutic implications, suggesting that interventions targeting thalamo-trigemino-cortical modulation (e.g., CGRP antagonists or neuromodulation devices) may alleviate photophobia.

While these insights advance our understanding of ictal photophobia, limitations must be acknowledged, including the small sample size. Although clinical variables including disease duration and time since attack onset were collected and explored, the limited sample size may have reduced statistical power to detect potential associations with neurophysiological parameters. Moreover, the focus on macular function may overlook peripheral retinal or full-field contributions, and the reliance on self-reported photophobia scales introduces subjectivity. Additionally, the study did not incorporate direct autonomic measures (e.g., heart rate variability or pupillometry), limiting confirmation of the proposed regulatory mechanism. Another possible limitation of our study is the lack of direct monitoring of pupil diameter that may have influenced ERG and VEP amplitudes and latencies. However, because the recording is focal and directed through the centre of the pupil, variations in overall pupil diameter have minimal impact on the effective retinal illuminance reaching the targeted central macular cones, in the presence of a steady equiluminant adapting background. Future research should incorporate a subgroup analysis of ictal patients not experiencing photophobia. This is to determine whether the observed S-cone VEP phase shifts are a specific biomarker for photophobia or a general physiological manifestation of the ictal migraine per se. Moreover, further research should integrate a multimodal approach, including direct ipRGCs assessments, autonomic biomarkers, and longitudinal tracking across migraine phases, to validate these findings and expand understanding of the modulation of visual pathways during photophobia symptoms.

Conclusions

Our study on patients with migraine recorded ictally reveals a selective reduction in B-Y 1F ERG amplitude vector, suggesting down-regulation of the S-cone pathway while sparing higher harmonics, B-R stimuli, and VEPs. This finding aligns with photic hypothalamic feedback. No significant correlations emerged between macular focal ERG parameters (amplitudes and phases for B-R and B-Y stimuli) and photophobia severity, indicating that macular cone-opponent pathways are not primary mediators of photophobia; instead, macular focal VEP phase for B-Y stimuli, despite being within the normal range, inversely correlated with photophobia severity scale suggesting subcortical-cortical mechanisms, such as thalamic-trigeminovascular convergence to sensory cortices, likely predominate, with implications for target therapies. Ultimately, our results underscore photophobia in migraine as a manifestation of an altered sensory integration beyond traditional visual circuits, where light may serve as a significant modulator of a complex, multidimensional neuronal network that controls homeostasis and intersects pain perception at the level of the trigeminal-thalamo-cortical nodes, adding complexity to its link with headache itself.

Article highlights

- Photophobia during a migraine attack is not directly correlated with variations in retinal or cortical electrophysiological responses.
- During a migraine attack, activity in photoreceptors sensitive to the short-wavelength light spectrum can vary.
- During a migraine attack, photophobia is associated with increased phase (e.g., latency) of cortical responses, suggesting cortico-subcortical integration mechanisms involving thalamo-trigeminovascular convergence onto the sensory cortices.

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Ethical considerations

The study protocol was approved by the local ethics committee, in accordance with the principles of the Declaration of Helsinki.

Consent to participate

Written informed consent was obtained from all participants

Consent for publishing

All authors agree that this article will be published in Cephalalgia.

Author contributions

F. Casillo: Conceptualization, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision.
A. Di Renzo: Formal analysis, Validation.
G. Sebastianelli: Writing – Review & Editing, Visualization
C. Abagnale: Writing – Review & Editing.
F. Martelli: Methodology.
C. Di Lorenzo: Visualization.
L. Ziccardi: Investigation.
B. Falsini: Methodology.
V. Parisi: Methodology, Funding Acquisition
G. Coppola: Methodology, Conceptualization, Writing – Original Draft, Writing – Review & Editing, Data Curation, Supervision.

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Declaration of conflicting interests

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

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Open practices

Not applicable

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