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Light-induced sensory dysregulation in migraine: Evidence from blink reflex habituation analysis

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Abstract

Background & Objective: Migraine involves altered brainstem sensory processing and photophobia affects 90% of patients. The blink reflex (BR) evaluates trigeminal-brainstem circuits non-invasively, but photic stimulation effects on BR habituation remain unexplored. This study aimed to investigate BR habituation changes following photic stimulation in episodic migraine patients versus healthy controls.
Methods: Thirty episodic migraine patients (ICHD-3 criteria) and 30 age-gender-matched controls underwent BR testing during interictal periods. Primary outcomes were changes in R1 amplitude and R2 areas (ipsilateral/contralateral) after standardized photic stimulation (6 Hz, 1200 cd/m², 60 seconds). Delta values (Δ = post-pre) were compared using Mann-Whitney U tests with Bonferroni correction.
Results: Baseline BR parameters were comparable between groups. Controls showed physiological habituation with increased R1 amplitude (median Δ = +42.3 μV) and reduced R2 areas (ipsilateral: -41.2 μV·ms, contralateral: -118.5 μV·ms). Migraine patients demonstrated impaired habituation with minimal R1 changes (+3.8 μV) and paradoxical R2 area increases (+2.4 and +31.7 μV·ms). All differences were significant ($p < 0.001$) with large effect sizes ($r = 0.72$-0.86).
Conclusion: Migraine patients exhibit profound BR habituation deficits following photic stimulation, reflecting brainstem sensory inhibition dysfunction. This approach may serve as an objective biomarker for migraine-related brainstem pathology.

Keywords: Migraine, blink reflex, habituation, brainstem, photophobia, sensory processing

INTRODUCTION

Migraine affects 12% of the global population and represents a leading cause of disability worldwide.[1] The disorder is characterized by recurrent headache episodes with photophobia, phonophobia, and nausea. Despite advances in migraine research, mechanisms underlying sensory hypersensitivity remain poorly understood.

Central sensitization and altered brainstem excitability are key pathophysiological features of migraine.[1,2] Habituation, the progressive response reduction to repeated stimuli, enables sensory filtering and prevents neural circuit overload.[3] Migraine patients exhibit interictal habituation deficits across multiple modalities including visual evoked potentials and auditory responses, reflecting cortical hyperexcitability and subcortical dysregulation.[4,5]

The blink reflex (BR) evaluates trigeminal afferents, brainstem interneurons, and facial efferents non-invasively.[6] BR consists of R1 (oligosynaptic pathway via main sensory trigeminal nucleus) and R2 (polysynaptic circuits involving spinal trigeminal nucleus and reticular formation). The R2 component is particularly sensitive to habituation and central modulation.

Previous BR studies in migraine reported inconsistent findings[7,8], but none examined photic stimulation effects despite photophobia's clinical prominence. Photophobia affects 80-90% of migraine patients and may persist interictally, suggesting persistent brainstem sensitization.

We hypothesized that migraine patients exhibit impaired BR habituation following photic stimulation, providing neurophysiological evidence for photophobia mechanisms. Our aims were to evaluate BR parameter changes after photic stimulation, compare habituation patterns between groups, and assess biomarker potential.

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METHODS

This case-control study enrolled 30 episodic migraine patients and 30 healthy controls at a tertiary headache center (January 2023-June 2024). Sample size calculation indicated 26 participants/group provided 90% power for detecting medium-large effects (Cohen's d = 0.75) with $\alpha = 0.05$.

Inclusion and exclusion criteria

The inclusion criteria were: Migraine diagnosis ≥12 months (ICHD-3 criteria), 2-8 attacks/month, age 18-65 years, interictal testing ≥72 hours from attacks.

The exclusion criteria were: Chronic migraine, medication overuse, neurological comorbidities, prophylactic medications, psychiatric disorders, pregnancy, recent hormonal contraceptive use.

Controls had no migraine history, neurological diseases, or family migraine history. Ethics committee approval and informed consent were obtained.

Electrophysiological recording

BR recordings used Nihon Kohden Neuropack X1 system in temperature-controlled (22-24°C), quiet, semi-darkened room (<10 lux). Surface electrodes (Ag/AgCl) were positioned bilaterally over orbicularis oculi with impedance <5 kΩ. Ground electrode placement was midline forehead.

Supraorbital nerve stimulation delivered constant current square-wave pulses (0.2 ms, 20-30 mA supramaximal intensity) with ≥30-second intervals. Sampling rate: 10 kHz, filtering: 20 Hz-2 kHz. Five consistent responses were averaged per condition.

Photic stimulation protocol

Grass PS33 Plus stimulator delivered white light flashes (6 Hz, 1200 cd/m², 60 seconds) from 30 cm distance. Participants maintained central fixation with eyes open. BR recordings were repeated immediately post-stimulation.

Statistical analysis

Primary outcomes: ΔR1 amplitude, ΔR2 areas (ipsilateral/contralateral). Mann-Whitney U tests compared groups with Bonferroni correction ($\alpha = 0.008$). Effect sizes calculated as $r = Z/\sqrt{N}$. IBM SPSS Statistics 28.0 was used.

RESULTS

Demographics

Migraine group: 30 patients (19 females, 11 males; mean age 35.2±8.4 years). Controls: 30 subjects (19 females, 11 males; mean age 36.8±9.2 years). No significant differences in age ($p = 0.421$) or gender distribution ($p = 1.000$). Migraine duration: 13.1±7.2 years, median attack frequency: 4/month. Photophobia present in 27/30 (90%) patients.

Baseline parameters

Pre-stimulation BR parameters showed no group differences: R1 latency (10.1±1.0 vs 9.9±0.8 ms, $p = 0.387$), R2 latency (30.8±3.1 vs 30.4±2.7 ms, $p = 0.543$), baseline amplitudes and areas (all $p > 0.25$).

Post-stimulation changes

Primary outcomes

ΔR1 amplitude: Controls showed robust facilitation (+42.3 μV, IQR: 22.1-58.7) while migraine patients had minimal change (+3.8 μV, IQR: -1.8-9.4, $p < 0.001$, $r = 0.72$).

ΔR2 area ipsilateral: Controls exhibited habituation (-41.2 μV·ms, IQR: -62.4 to -23.8) versus absent habituation in migraine (+2.4 μV·ms, IQR: -6.7 to +15.1, $p < 0.001$, $r = 0.78$).

ΔR2 area contralateral: Controls showed substantial reduction (-118.5 μV·ms, IQR: -152.3 to -89.7) while migraine patients had paradoxical increases (+31.7 μV·ms, IQR: +12.3 to +52.1, $p < 0.001$, $r = 0.86$).

Secondary outcomes

Latency changes were nonsignificant ($p > 0.1$). R2 amplitude facilitation occurred in controls (+32.1 μV) but not migraine patients (+2.9 μV, $p < 0.001$).

DISCUSSION

Main findings

Migraine patients exhibited profound BR habituation deficits after photic stimulation, with absent R1 facilitation and paradoxical R2 increases. Preserved latencies indicate intact conduction pathways, while amplitude/area changes suggest selective dysfunction of

Figure 1.

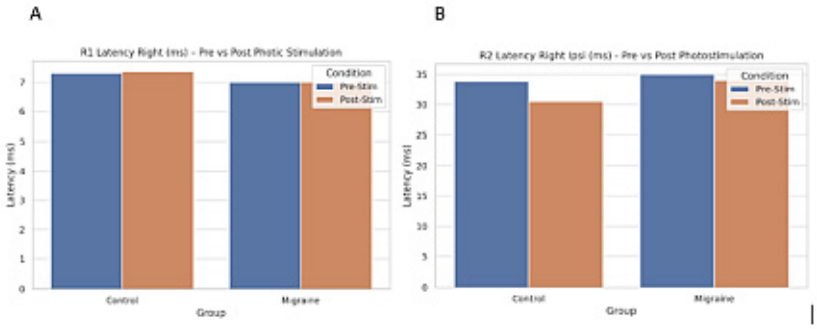

Figure 1. Baseline blink reflex parameters showing comparable R1 and R2 latencies, amplitudes, and areas between migraine patients and healthy controls (all $p > 0.05$), confirming adequate group matching.

Figure 2.

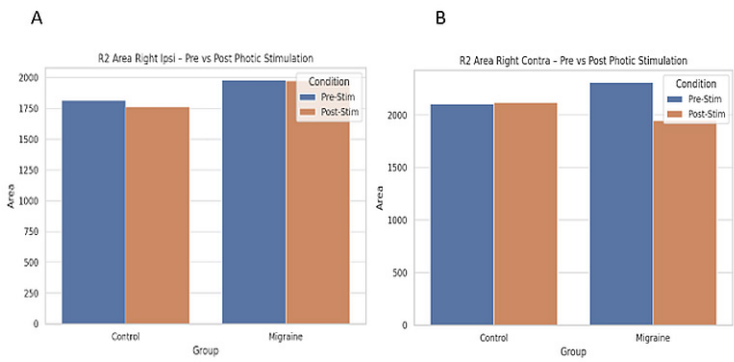

Figure 2. Changes in R2 area (ipsilateral and contralateral) following photic stimulation. Controls show habituation (decreased areas) while migraine patients demonstrate paradoxical increases, indicating impaired brainstem inhibition ($p < 0.001$ for both comparisons).

Figure 3

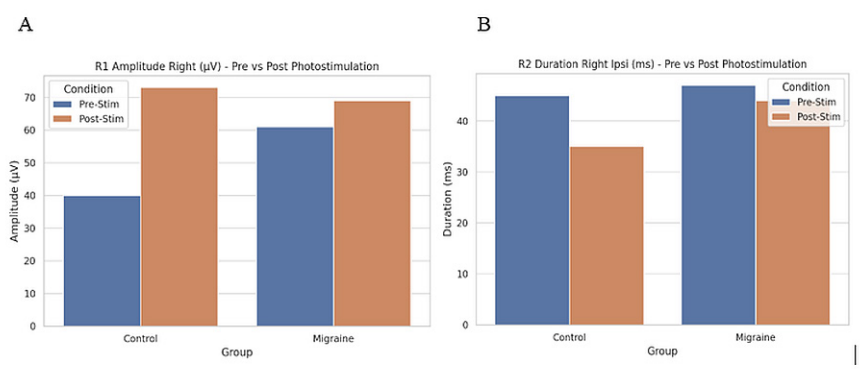

Figure 3. R1 amplitude and R2 duration changes after photic stimulation. Controls exhibit facilitation and appropriate modulation, while migraine patients show minimal changes, reflecting deficient brainstem sensory processing.

Table 1: Demographic and clinical characteristics

Characteristic	Migraine (n=30)	Controls (n=30)	p-value
Age (years), mean ± SD	35.2 ± 8.4	36.8 ± 9.2	0.421
Female sex, n (%)	19 (63.3)	19 (63.3)	1.000
Migraine duration (years)	13.1 ± 7.2	-	-
Attack frequency/month, median (IQR)	4 (3-6)	-	-
HIT-6 score, mean ± SD	61.2 ± 9.1	-	-
Photophobia, n (%)	27 (90)	-	-
Phonophobia, n (%)	24 (80)	-	-
Nausea, n (%)	23 (77)	-	-
Aura, n (%)	9 (30)	-	-

HIT-6: Headache Impact Test-6; IQR: Interquartile Range

Table 2: Blink reflex parameters before and after photic stimulation

Parameter	Migraine (n=30)	Controls (n=30)	p-value
R1 Amplitude (μV)			
Pre-stimulation	238 ± 61	241 ± 55	0.817
Post-stimulation	242 ± 59	283 ± 58	0.003*
Δ (Post-Pre), median (IQR)	+3.8 (-1.8 to +9.4)	+42.3 (22.1 to 58.7)	<0.001†
R2 Area Ipsilateral (μV·ms)			
Pre-stimulation	152 ± 42	149 ± 39	0.756
Post-stimulation	155 ± 41	108 ± 31	<0.001*
Δ (Post-Pre), median (IQR)	+2.4 (-6.7 to +15.1)	-41.2 (-62.4 to -23.8)	<0.001†
R2 Area Contralateral (μV·ms)			
Pre-stimulation	294 ± 73	307 ± 79	0.512
Post-stimulation	326 ± 78	189 ± 52	<0.001*
Δ (Post-Pre), median (IQR)	+31.7 (+12.3 to +52.1)	-118.5 (-152.3 to -89.7)	<0.001†
R1 Latency (ms)			
Pre-stimulation	10.1 ± 1.0	9.9 ± 0.8	0.387
Δ (Post-Pre), median (IQR)	+0.08 (-0.2 to +0.3)	+0.12 (-0.1 to +0.4)	0.431
R2 Latency (ms)			
Pre-stimulation	30.8 ± 3.1	30.4 ± 2.7	0.543
Δ (Post-Pre), median (IQR)	+0.31 (-0.4 to +1.1)	+0.18 (-0.3 to +0.7)	0.287

*$p < 0.05$; †$p < 0.001$ (Bonferroni corrected); Δ: Delta (change); IQR: Interquartile Range

modulatory interneurons.

These findings extend previous habituation deficit observations in migraine[4,5] and provide the first evidence linking photophobia to measurable brainstem dysfunction. The large effect sizes suggest strong discriminatory power for clinical applications.

Neurophysiological mechanisms

Habituation deficits likely reflect dysfunction within trigeminal sensory processing circuits and reticular formation. Normal R2 habituation requires intact inhibitory mechanisms within the spinal trigeminal nucleus.[9] The failure of habituation, particularly following photic stimulation, suggests impaired inhibitory modulation consistent with altered excitatory-inhibitory balance in migraine.

The specific photosensitivity may reflect known connections between retinal pathways and trigeminal processing centers. Photosensitivity in migraine may be explained by intrinsically photosensitive retinal ganglion cells (ipRGCs), which send projections to brainstem nuclei that modulate trigeminal sensory processing.[10] This neural connection may underlie both the clinical photophobia observed in migraine and our electrophysiological findings of altered blink reflex habituation.

Clinical significance

These findings offer several clinical applications: (1) objective migraine biomarker for atypical presentations, (2) treatment response monitoring tool, and (3) research stratification method. The non-invasive nature and standard equipment availability make this approach clinically feasible.

Recent studies suggest that successful migraine prophylaxis may normalize habituation deficits[11], supporting the utility of this approach for treatment monitoring. The standardized protocol ensures reproducibility across centers.

Comparison with literature

Our findings align with established habituation deficit concepts in migraine.[4,5] De Marinis *et al*. reported reduced BR habituation in chronic migraine[12], while Di Clemente *et al*. demonstrated interictal deficits in nociceptive blink reflexes.[13] Our study uniquely examines light-induced changes, providing direct relevance to photophobia symptoms.

The robust effect sizes observed exceed those typically reported in migraine neurophysiology studies, suggesting that photic stimulation may unmask habituation deficits more effectively than standard protocols.

Study limitations

The single-center design and moderate sample size limit generalizability. Cross-sectional design prevents assessment of temporal stability. We did not control for menstrual cycle phase, which may influence blink reflex parameters. Future multicenter studies with larger cohorts and longitudinal designs are needed.

Another limitation of the study was that the findings were not related to headache severity, disability scores, or assessments of photophobia. There is therefore less clinical correlation than the ideal. However, correlation studies between BR parameters and clinical severity measures could enhance clinical utility. Investigation of chronic migraine patients and ictal period testing would provide comprehensive understanding of BR abnormalities across migraine spectrum.

Future directions

Planned investigations include: (1) multicenter validation with larger cohorts, (2) longitudinal assessment of habituation stability, (3) correlation with validated severity scales, (4) evaluation in chronic migraine and other headache types, and (5) treatment response monitoring studies.

Integration with other neurophysiological techniques (transcranial magnetic stimulation, functional neuroimaging) could provide multimodal insights into migraine pathophysiology and enhance biomarker development.

Conclusion

Migraine patients demonstrate significantly impaired blink reflex habituation following photic stimulation, characterized by absent R1 facilitation and paradoxical R2 increases. These findings provide objective electrophysiological evidence of defective brainstem sensory inhibition and support central sensitization theories in migraine pathophysiology.

BR habituation testing under photic stimulation represents a feasible, non-invasive approach for assessing brainstem dysfunction in migraine. The large effect sizes and standardized protocol support its potential as a valuable biomarker for diagnosis, treatment monitoring, and research applications in migraine and related disorders.

DISCLOSURE

Data availability: Deidentified data are available upon reasonable request.

Financial support: None

Conflicts of interest: None

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