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Eccentricity Dependency of Retinal Electrophysiological Deficits in People With Episodic Migraine

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Purpose. During the non-attack period, people with migraine may show retinal dysfunction. This study builds on previous work by exploring the possibility of foveal and non-foveal visual field and electroretinographic deficits and determining the overlap in eccentricity of such localized visual deficits in people with migraine.

Methods. Visual fields and multifocal electroretinography (mf-ERG) were tested in 27 people with migraine (aged 19–45 years) and 18 non-headache controls (aged 20–46 years). Data were averaged according to 5 concentric rings at < 1.5 degrees (foveal) and 5 degrees, 10 degrees, 15.5 degrees, and 22 degrees eccentricities (non-foveal). Linear mixed effects modelling was used to predict mf-ERG amplitude, mf-ERG peak time, and visual field sensitivity with fixed effects of eye, group, and eccentricity.

Results. Foveal mf-ERG responses, and visual field sensitivity across all eccentricities (foveal and non-foveal) were similar between the migraine and control groups ($P > 0.05$). In contrast, the non-foveal mf-ERG was reduced in amplitude in people with migraine relative to controls ($P < 0.001$), and this group difference depended on eccentricity ($P < 0.001$) – most prominently, in the parafoveal region (ring 2, $P = 0.001$).

Conclusions. Retinal electrophysiological deficits were observed in people with migraine in the parafoveal region (between 1.5 degrees and 5 degrees eccentricity), without corresponding visual field deficits. This suggests a spatially localized area of retinal neuronal dysfunction in people with migraine that is insufficient to manifest as a visual field sensitivity loss using standard perimetric methods. Our study highlights the added confound of migraine when conducting standard clinical retinal electrophysiological tests for conditions such as glaucoma, particularly non-foveally.

Keywords: multifocal electroretinography (mf-ERG), visual field, interictal, parafoveal, headache

Migraine is a debilitating primary headache disorder affecting 10% to 15% of people worldwide.[1] While headache is a prominent feature, migraine is also associated with gastrointestinal disturbances (nausea and/or vomiting) and sensory sensitivity (photophobia and phonophobia).[2] Visual symptoms like mild blurred vision can occur during a migraine attack (known as the ictal period), and approximately 20% to 30% of people have migraine with aura, which are short-lasting reversible neurological disturbances that are predominantly visual (e.g. a scintillating scotoma) and typically precede the headache. However, outside the attack when a person is asymptomatic (known as the interictal period), standard clinical tests of vision may yield abnormal results. Visual field defects have been found in 20% to 60% of people with migraine interictally.[3–13] The visual field defects are not a remnant of aura (i.e. occurring even in people who never suffer aura symptoms) and are variable in their timing and severity (i.e. worse closer to a migraine attack[13,14] and can decrease in severity over time[5]).

Most visual field defects in people with migraine are spatially localized (i.e. not a generalized loss in sensitivity across the visual field) and monocular (i.e. appear retinal in origin), which is especially intriguing in the context of differential diagnosis with glaucoma. Risk factors that affect the prevalence or incidence of glaucoma can help identify populations that might be targeted and tested for early detection and management of glaucoma. The balance of evidence suggests that a history of migraine increases the risk of developing glaucoma,[15–32] although not all studies report an association.[33–40] In particular, migraine has been associated with faster visual field deterioration in normal-tension glaucoma, suggesting a target for more frequent monitoring and more aggressive anti-glaucoma therapy.[41]

As such, previous studies of vision and ocular health in people with migraine seek to explore clinical parameters that are known to be abnormal in glaucoma, using visual field tests, retinal imaging, and/or visual electrophysiology. One such study by Verroiopoulos et al.[42] conducted a suite

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of clinical visual tests: optical coherence tomography (OCT), flash electroretinography (ERG), visual evoked potentials, and multifocal electroretinography (mf-ERG), but not visual field testing. The authors reported two significant differences between the migraine and control groups. First, they found subtle circumpapillary retinal nerve fiber layer thinning (approximately 4–5 µm) in people with migraine relative to controls.[42] This OCT finding has been widely reported and established in recent systematic reviews and meta-analyses of cross-sectional studies of people with migraine,[43,44] and therefore needs not be replicated.

The second, novel finding by Verroiopoulos et al.[42] was reduced mf-ERG responses at the central ring (i.e. foveally) in people with migraine relative to controls, but at no other eccentricity. Compared to the traditional full-field ERG, the mf-ERG technique allows recording of electrophysiological responses from multiple discrete areas as a topographical representation of retinal electrical activity.[45,46] Their finding[42] suggests that full stimulation of the retina is insensitive to subtle and localized electrophysiological deficits at the fovea in people with migraine. However, this result remains unreplicated, as no other study has tested the mf-ERG in people with migraine. An exclusively foveal electrophysiological deficit, however, seems at odds with the plethora of reports of non-foveal visual field defects in people with migraine that are apparent on 24-2 testing.[3–13] Here, we explore the possibility of foveal and non-foveal visual deficits in people with migraine, using both visual fields and electrophysiology. This study builds on previous work by determining the overlap in eccentricity of localized visual deficits in people with migraine.

Specifically, we superimposed the ring analysis approach of mf-ERG on fundus-tracked visual field testing to match the spatial extent of retinal electrophysiology (up to 22 degrees eccentricity) and visual field testing (up to 21 degrees eccentricity). We also combined the 24-2 pattern with added test locations in the 10 degrees region, because central early glaucomatous visual field defects can be detected with a denser grid that are not observed on 24-2 testing.[47] Because spatially localized visual field defects in migraine have been reported non-foveally,[6] and retinal electrophysiological deficits have been detected foveally,[42] we predicted that migraine would be associated with visual field and mf-ERG deficits at foveal and non-foveal eccentricities.

Methods

Participants

The study was approved by the Human Research Ethics Committee of The University of Melbourne (ID #1443394). Written informed consent, according to the tenets of the Declaration of Helsinki, was obtained from participants who were recruited by word-of-mouth, advertisements across The University of Melbourne, and through a database of previous research participants.

To our knowledge, only one study reports mf-ERG results in people with migraine,[42] and these data were used to perform our power analysis in G*Power.[48] Sixteen participants per group provided a power of 90% for detecting a 1-tailed reduction in the foveal mf-ERG response (at a conservative estimate of half the effect size of Cohen's $d = 2.12$ reported by Verroiopoulos et al.[42]) in people with migraine compared to non-headache controls ($\alpha = 0.05$). To account for potential data attrition, we recruited 27 people with migraine (aged 19–45 years, mean ± standard deviation = 29 ± 8 years, 18 with migraine without aura, and 9 with migraine with aura to reflect typical population prevalences of the 2 most common forms of migraine) and 18 non-headache control participants (aged 20–46 years, 31 ± 7 years). Control participants had never experienced a migraine and were free from regular headaches (less than 4 in the past year). Migraine participants were required to meet the diagnostic criteria of migraine without aura (classification 1.1) or migraine with aura (specifically, "typical aura with headache," classification 1.2.1.1) according to the International Classification of Headache Disorders.[2]

All participants were examined to ensure the following inclusion criteria: best corrected visual acuity of 6/7.5 or better, refractive error within ±5.00 diopters (D) sphere and −2.00 D astigmatism, no history of ocular surgery or trauma (including laser refractive surgery), normal ocular health findings on slit lamp biomicroscopy, fundus lens examination and retinal photography, and no systemic conditions or medications known to affect visual function or neurological state, including prophylactic migraine medications.

Migraine participants were tested at least 24 hours after the end of a migraine attack to minimize residual effects of acute medications and the possible influence of transient post-migraine fatigue or nausea. Migraine participants completed the Migraine Disability Assessment Score (MIDAS) questionnaire to determine the impact of migraine on tasks of daily living over the past 3 months.[49,50] The MIDAS questionnaire scores range from minimal disability (grade 1 = score 0–5), mild (grade 2 = score 6–10), moderate (grade 3 = score 11–20), to severe disability (grade 4 = score 21+). Information about their migraine attacks was ascertained through a written custom headache questionnaire and clinical interview, including age at first migraine, migraines in past year, and days since last migraine.

After the vision screening and questionnaires, all participants completed the same order of procedures for both eyes (the right eye before the left eye): (1) pupillary dilation, (2) mf-ERG recording, and (3) visual field testing.

Multifocal Electroretinography

The mf-ERG was recorded and analyzed according to the International Society for Clinical Electrophysiology of Vision standards[45] using the VERIS system (Electro-Diagnostic Imaging Inc., Milpitas, CA, USA) connected to a 23.6-inch light-emitting diode monitor for stimulus display (ASUS model VE247H, 1920 × 1080 pixel resolution, 60 hertz [Hz] frame rate). A Fresnel lens was placed in front of the stimulus display monitor to ensure brightness uniformity.

Pupils were dilated to ≥ 6 mm diameter with one drop each of 1% tropicamide and 2.5% phenylephrine. Forehead skin was prepared with 70% isopropyl alcohol and pumice (Professional Disposables Inc., Orangeburg, NY, USA). Active Dawson-Trick-Litzkow electrodes were placed at the lower corneal limbus and referenced to the ipsilateral canthus with silver-silver chloride electrodes (Viasys Healthcare, Madison, WI, USA). A silver-silver chloride skin electrode (Viasys Healthcare, Madison, WI, USA) served as common ground on the forehead midline. Electrode impedance was kept below 5 kΩ. Signals were amplified (50,000-fold) and filtered with low- and high-frequency cutoffs of 10 Hz and 300 Hz, respectively (IngEnesi A10 preamplifier; Rome, Italy). No notch filter or spatial averaging was used.

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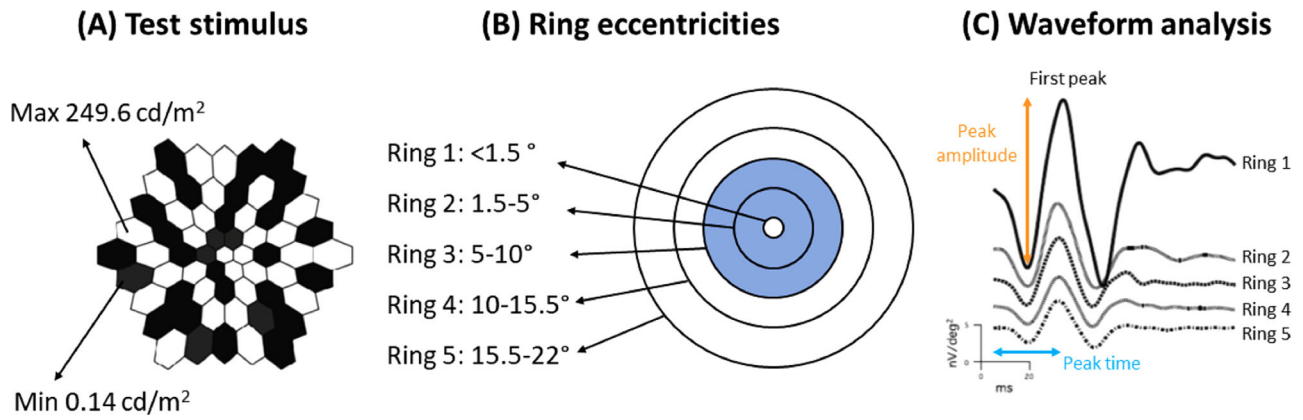


Figure 1. Schematic of mf-ERG methodology. (**A**) The stimulus array fell within the central 44 degrees diameter (up to 22 degrees eccentricity). (**B**) Hexagons were arranged in five rings, scaled for eccentricity, and responses were averaged within each ring for analysis. (**C**) Averaged waveforms for each ring were analyzed for peak-to-peak amplitude and peak time relative to total ring area.

The test stimulus consisted of 61 hexagons scaled for retinal eccentricity (Fig. 1A) with a total diameter of 44 degrees. An m-sequence of 2^{13}–1 steps controlled the temporal sequence of change between light (249.6 cd/m^2) and dark stages (0.14 cd/m^2) of each stimulus hexagon (Michelson contrast = 99.9%). Participants wore their appropriate refractive correction for the 40 cm working distance and fixated on the on-screen central red target. Each recording (total 4 minutes) was divided into 32 segments to allow the participant to blink and rest between segments. Poor recording segments (from noise, eye movements, and/or excessive blinking) were manually discarded and re-recorded. Two 4-minute recordings were obtained for each eye separately and averaged for analysis. An opaque patch was used to cover the eye not being stimulated. First-order responses were automatically pooled into 5 concentric rings by the VERIS software (Fig. 1B): ring 1 (< 1.5 degrees eccentricity), ring 2 (1.5 to 5 degrees eccentricity), ring 3 (5 to 10 degrees eccentricity), ring 4 (10 to 15.5 degrees eccentricity), and ring 5 (15.5 to 22 degrees eccentricity). Amplitude was taken as the peak-to-peak N1 to P1 amplitude (in nV) between the initial negative component (N1) and positive component (P1), and peak time (in ms) was taken from stimulus onset to the first positive peak P1 (Fig. 1C).

Visual Field Testing

White-on-white automated perimetry with size III Goldmann stimuli (0.43 degrees diameter) was conducted using the Compass perimeter with fundus and pupil size tracking (CenterVue, Padova, Italy), standard background luminance of 31.5 asb, and maximum luminance of 10,000 asb. Participants completed the New Grid test with ZEST thresholding strategy, which includes all 52 non-blindspot locations of the 24-2 grid, the fovea, and an additional 12 macular locations for increased central visual field density (i.e. total 65 non-blindspot locations). Only visual field test results with reliability indices (false positive and false negative rates) < 25% were included in the analysis. The investigator also manually checked that an average pupil size of ≥ 4 mm was maintained throughout the visual field testing. For ring analysis, the two farthest temporal locations (at 27 degrees eccentricity) were discarded. For the remaining 63 locations, pointwise visual field sensitivities (dB) were averaged according to the same 5 concentric rings as per the mf-ERG (see Fig. 1B) up to a maximum of 21 degrees eccentricity of the 24-2 pattern.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.2,[51] with the lme4 package for linear mixed effects modeling.[52] Data were tested for normality using a Kolmogorov-Smirnov test. The migraine group and the non-headache control group demographics were compared using independent group tests (*t*-tests, chi-square test of proportions, or Mann-Whitney rank sum tests, as appropriate). Pearson correlation coefficients (for normally distributed data) or Spearman rank correlation coefficients (for data that violated the assumption of normality) were calculated to explore the relationship between visual deficits and migraine characteristics in the migraine group only. As mf-ERG responses and visual field sensitivity are substantially higher foveally than non-foveally, and because ring 1 data consisted of only one estimate per participant (whereas rings 2 to 5 data were averaged across at least 8 retinal locations), foveal and non-foveal data were analyzed separately. Data from both eyes were included. Linear mixed effects modeling was conducted to determine the extent to which the mf-ERG (peak amplitude and peak time) and visual field (sensitivity) outcome measures are accounted for by the possible random effect of participant, and fixed effects of group (migraine or control), eye (left or right), and for the non-foveal data, eccentricity (rings 2 to 5). The *P* values for multiple pairwise comparisons were adjusted using the Tukey method. A *P* value of 0.05 was the criterion for statistical significance.

Results

Participants

Demographic information of the participant groups appears in Table 1, showing no differences between the migraine and non-headache control groups in their clinical characteristics ($P > 0.05$).

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Table 1. Clinical Characteristics and Visual Field Test Results of the Participant Groups (Migraine Versus Non-Headache Control Participants)

	Migraine	Control	*P* Value
No. of subjects	27	18	
Age, y, mean ± standard deviation	31 ± 7	29 ± 8	t(43) = 0.95, $P = 0.35$
Gender, M:F	7:20	9:9	χ^2 (1) = 0.10
Spherical equivalent refractive error, D, median [range]	−0.25 [−4.5 to +1.5]	−0.50 [−5.0 to 0.0]	U = 195, $P = 0.26$
Average pupil size, mm, mean ± standard deviation during visual field testing	5.6 ± 0.5	5.8 ± 0.5	t(43) = 0.93, $P = 0.36$
Mean defect, dB, mean ± standard deviation	−0.24 ± 0.81	−0.20 ± 0.57	t(43) = 0.18, $P = 0.86$
Pattern standard deviation, dB, mean ± standard deviation	1.89 ± 0.33	1.80 ± 0.19	t(43) = 1.00, $P = 0.32$
Foveal visual field sensitivity, dB, median [range]	36 [30 to 39]	37 [33 to 39]	U = 223.5, $P = 0.65$
Days since last migraine, median [range]	10 [1 to 270]	—	—
Age at first migraine, y, mean ± standard deviation	18 ± 7	—	—
Migraines in past year, median [range]	8 [1 to 48]	—	—
Estimated number of lifetime attacks, median [range]	96 [2 to 960]	—	—
MIDAS questionnaire score, median [range]	8 [0 to 43]	0 [0 to 0]	—

P values are the results of the statistical comparisons between groups (*t*-tests, chi-square test of proportions, and Mann-Whitney rank sum tests).

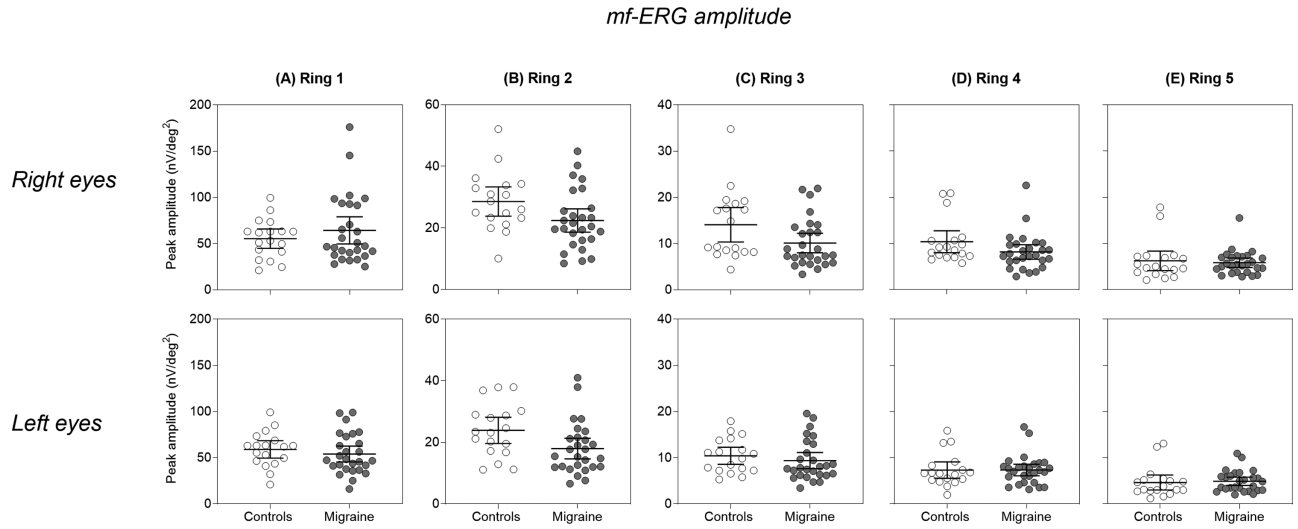


Figure 2. Ringwise mf-ERG peak amplitude for the non-headache control (unfilled) and migraine (filled) groups at (**A**) ring 1 at < 1.5 degrees eccentricity, (**B**) ring 2 at 1.5 degrees to 5 degrees eccentricity, (**C**) ring 3 at 5 degrees to 10 degrees eccentricity, (**D**) ring 4 at 10 degrees to 15.5 degrees eccentricity, and (**E**) ring 5 at 15.5 degrees to 22 degrees eccentricity. Individual data are shown with the group mean ± 95% confidence intervals of the mean.

Foveal Multifocal Electroretinography

For the foveal mf-ERG data (ring 1, < 1.5 degrees eccentricity), a linear mixed effects model was used to predict mf-ERG amplitude (Fig. 2A; 18 control and 27 migraine) with "eye" and "group" (formula: amplitude ~ eye + group + eye × group), including participant as a random effect (for the full linear mixed effects modeling results, see Supplementary Material A, Table S1). There was no difference in mf-ERG peak amplitude between the migraine and control participants (effect of group: $\beta = -5.02$, 95% confidence interval [CI] = −24.0 to 14.0, $P = 0.60$) and no difference between right and left eyes (effect of eye: $\beta = 12.24$, 95% CI = −6.09 to 30.6, $P = 0.19$). The same approach was taken for fitting a linear mixed effects model (see Supplementary Material A, Table S2) for foveal mf-ERG peak time (Fig. 3A; 18 control and 27 migraine). No overall effect of eye was observed (effect of eye: $\beta = -0.21$, 95% CI = −2.41 to 1.98, $P = 0.85$) and there was no group difference in peak times between migraine and non-headache control groups foveally (effect of group: $\beta = -0.55$, 95% CI = −2.69 to 1.60, $P = 0.61$).

Non-Foveal Multifocal Electroretinography

We fitted a linear mixed model to predict non-foveal mf-ERG amplitude (Figs. 2B–E; 18 control and 27 migraine) with "eccentricity," "eye," and "group" (formula: amplitude ~ eccentricity + eye + group + eccentricity × group), including participant as a random effect (for the full linear mixed effects modeling results; see Supplementary Material A, Table S3). As expected, peak amplitude decreased as retinal eccentricity increased (effect of ring 3: $\beta = -13.98$, 95% CI = −16.19 to −11.76, $P < 0.001$; effect of ring 4: $\beta = -17.39$, 95% CI = −19.61 to −15.17, $P < 0.001$; and effect of ring 5: $\beta = -20.80$, 95% CI = −23.01 to −18.58, $P < 0.001$). We also found a consistent bias toward greater mf-ERG amplitudes for right eyes across all non-foveal eccentricities (effect of eye: $\beta = 2.34$, 95% CI = 1.35

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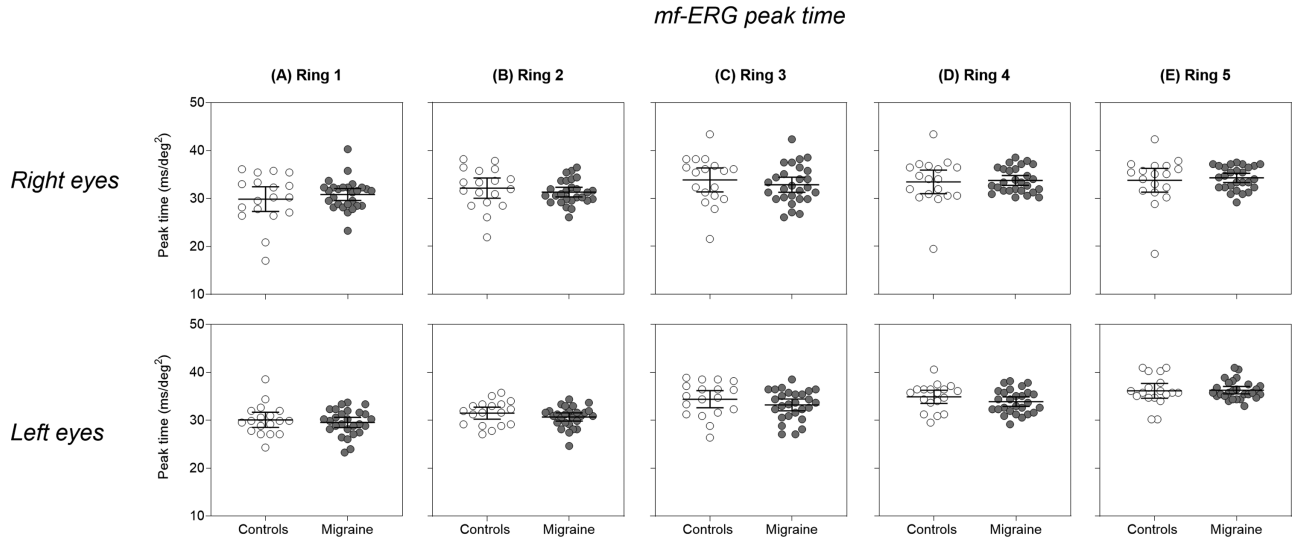


Figure 3. Ringwise mf-ERG peak times for the non-headache control (unfilled) and migraine (filled) groups at (**A**) ring 1 at < 1.5 degrees eccentricity, (**B**) ring 2 at 1.5 degrees to 5 degrees eccentricity, (**C**) ring 3 at 5 degrees to 10 degrees eccentricity, (**D**) ring 4 at 10 degrees to 15.5 degrees eccentricity, and (**E**) ring 5 at 15.5 degrees to 22 degrees eccentricity. Individual data are shown with the group mean ± 95% confidence intervals of the mean.

Table 2. Correlation Coefficients Describing the Relationship Between (A) the Right Eyes and (B) the Left Eyes mf-ERG Amplitude at Ring 2 and Migraine Characteristics (n = 27 Migraine Participants).

	(A) Right Eyes	(B) Left Eyes
Days since last migraine	Spearman $r = -0.12$, $P = 0.56$	Spearman $r = -0.12$, $P = 0.57$
Age at first migraine	Pearson $r = 0.24$, $R^2 = 0.06$, $P = 0.25$	Pearson $r = 0.24$, $R^2 = 0.06$, $P = 0.25$
Migraines in past year	Spearman $r = -0.02$, $P = 0.91$	Spearman $r = 0.19$, $P = 0.35$
Estimated number of lifetime attacks	Spearman $r = -0.06$, $P = 0.79$	Spearman $r = 0.13$, $P = 0.52$
MIDAS questionnaire score	Spearman $r = -0.25$, $P = 0.21$	Spearman $r = 0.01$, $P = 0.97$

to 3.33, $P < 0.001$). In addition, the overall effect of group (migraine versus control) was statistically significant, with lower peak amplitudes in the migraine participants relative to non-headache controls (effect of group: $\beta = -6.04$, 95% CI = −8.86 to −3.21, $P < 0.001$). There was a significant interaction between group and eccentricity (effect of ring 3 × group: $\beta = 3.54$, 95% CI = 0.67 to 6.40, $P = 0.016$; effect of ring 4 × group: $\beta = 4.95$, 95% CI = 2.08 to 7.81, $P < 0.001$; and effect of ring 5 × group: $\beta = 5.96$, 95% CI = 3.10 to 8.83, $P < 0.001$). Tukey multiple pairwise comparisons indicated that mf-ERG amplitudes in people with migraine were significantly smaller than the control group parafoveally, at ring 2 (see Fig. 2C; at 1.5 degrees to 5 degrees eccentricity, $P = 0.001$; see Supplementary Material A, Table S4 for results of all pairwise comparisons). None of the migraine features in our cohort, such as migraine history, severity, or frequency, predicted this parafoveal reduction in mf-ERG amplitude ($P > 0.05$; Table 2).

Similarly, non-foveal mf-ERG peak times were fitted with a linear mixed effects model (see Supplementary Material A, Table S5). Peak times were more delayed with increasing eccentricity for both migraine and control groups (effect of ring 3: $\beta = 2.31$, 95% CI = 1.11 to 3.52, $P < 0.001$; effect of ring 4: $\beta = 2.36$, 95% CI = 1.16 to 3.57, $P < 0.001$; and effect of ring 5: $\beta = 3.15$, 95% CI = 1.95 to 4.36, $P < 0.001$). Consistent with our overall finding of lower mf-ERG amplitudes in the left eyes, we found relatively delayed (increased) peak times compared to the right eyes across all participants (effect of eye: $\beta = -0.66$, 95% CI = −1.20 to −0.12, $P < 0.001$). There was no difference, however, between the migraine and control groups in non-foveal mf-ERG peak time across all eccentricities (effect of group: $\beta = -0.81$, 95% CI = −2.47 to 0.84, $P = 0.33$).

Foveal Visual Field Sensitivity

Foveal visual field data for one control participant was missing due to technical issues on the day of testing. In addition, we excluded data from one control and three migraine participants whose visual field test result in either eye was unreliable (> 25% false positives/negatives). As per the mf-ERG data, we fitted a linear mixed model to the foveal visual field sensitivity data (ring 1, < 1.5 degrees eccentricity; Fig. 4A; 16 control and 24 migraine) with "eye" and "group" (formula: sensitivity ~ eye + group + eye × group), including participant as a random effect (for the full linear mixed effects modeling results; see Supplementary Material A, Table S6). Neither eye (effect of eye: $\beta = 0.41$, 95% CI = −1.20 to −0.12, $P = 0.46$) nor group (effect of group: $\beta = -0.14$, 95% CI = −1.20 to −0.12, $P = 0.80$) were significant fixed effects, indicating that foveal visual field sensitivity was similar across all participants.

Non-Foveal Visual Field Sensitivity

Figures 4B to 4E depict the non-foveal visual field sensitivity for each eye (17 control and 24 migraine participants). From our linear mixed effects modeling (see Supplementary Material A, Table S7), we found peak amplitude decreased as reti-

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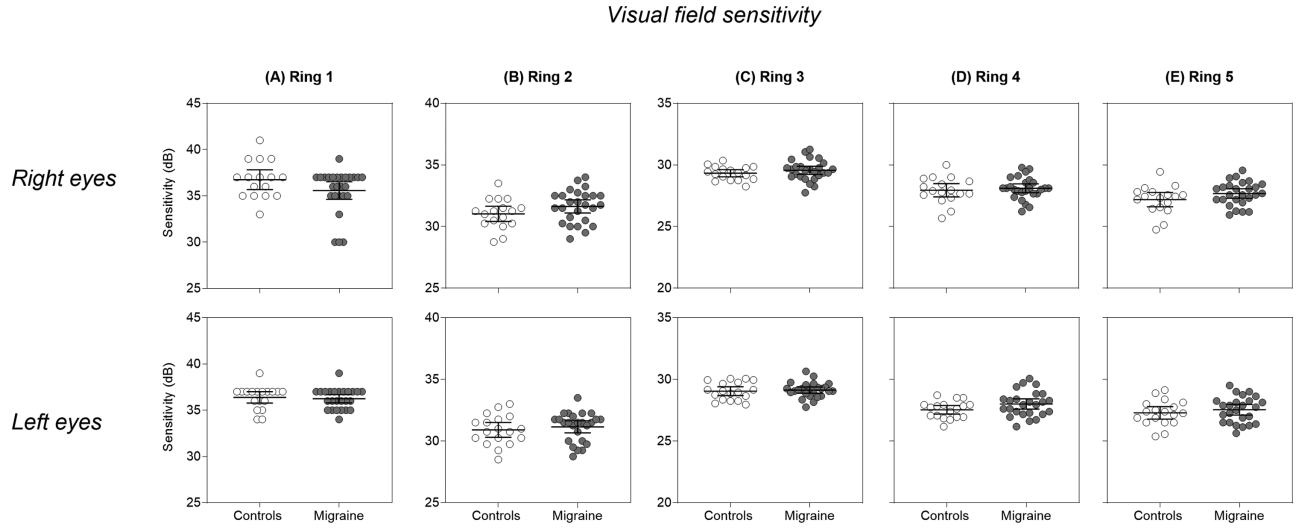


Figure 4. Ringwise visual field sensitivity for the non-headache control (unfilled) and migraine (filled) groups at (**A**) ring 1 at < 1.5 degrees eccentricity, (**B**) ring 2 at 1.5 degrees to 5 degrees eccentricity, (**C**) ring 3 at 5 degrees to 10 degrees eccentricity, (**D**) ring 4 at 10 degrees to 15.5 degrees eccentricity, and (**E**) ring 5 at 15.5 degrees to 22 degrees eccentricity. Individual data are shown with the group mean ± 95% confidence intervals of the mean.

Table 3. Summary of Estimated Marginal Means ± 95% Confidence Limits Derived From the Linear Mixed Effects Model for Each Group Comparison of mf-ERG Amplitude, mf-ERG Peak Time, and Visual Field Sensitivity

Comparison	Group	Estimated Marginal Mean	Standard Error	Degrees of Freedom	Lower Confidence Limit	Upper Confidence Limit
mf-ERG amplitude	Control	13.2	0.874	43	11.41	14.9
	Migraine	10.7	0.713	43	9.31	12.2
mf-ERG peak time	Control	33.8	0.532	43	32.7	34.8
	Migraine	33.3	0.435	43	32.4	34.2
Visual field sensitivity	Control	28.8	0.178	42.7	28.4	29.1
	Migraine	29.1	0.146	43.1	28.8	29.4

Results are averaged over the levels of "eccentricity" (ring) and "eye". The Kenward-Roger approach was used to estimate the degrees of freedom.

nal eccentricity increased (effect of ring 3: $\beta = -1.78$, 95% CI = −2.11 to −1.46, $P < 0.001$; effect of ring 4: $\beta = -3.23$, 95% CI = −3.56 to −2.90, $P < 0.001$; and effect of ring 5: $\beta = -3.73$, 95% CI = −4.06 to −3.40, $P < 0.001$). There was a consistent bias toward greater visual field sensitivity for right eyes across all non-foveal eccentricities (effect of eye: $\beta = 0.23$, 95% CI = 0.08 to 0.38, $P = 0.003$). However, there was no group difference in non-foveal visual field sensitivity (effect of group: $\beta = 0.40$, 95% CI = −0.12 to 0.92, $P = 0.13$). A summary of the estimated marginal means derived from the linear mixed effects modeling for each group comparison of mf-ERG amplitude, mf-ERG peak time, and visual field sensitivity is shown in Table 3.

Discussion

We found people with migraine showed reduced mf-ERG amplitude in the parafoveal region compared to the non-headache control group, suggesting an eccentricity-dependent pattern of retinal dysfunction that is detectable using standard electrophysiological approaches.[45] The mf-ERG deficits in people with migraine could occur in the absence of localized visual field defects. Example representative mf-ERG and visual field test results are shown in Supplementary Material B, highlighting that mf-ERG amplitude can be abnormally reduced parafoveally (by approximately 20%) in people with migraine (Supplementary Fig. S1), yet visual field performance may be similar between migraine and control participants (Supplementary Fig. S2).

Our study was motivated by previous reports of spatially localized mf-ERG deficits[42] and monocular visual field defects (see review in Ref. 6) that appear to be indistinguishable between migraine with and without aura groups. Hence, we recruited people with migraine into a single group to compare with non-headache controls. In the context of a retinal study, the presence of aura is unlikely to influence whether a person with migraine presents with a retinal deficit, given that the neurological substrate for migraine aura is considered cortical in origin.[53] On the other hand, the origins of the human mf-ERG are understood to be retinal, and multifactorial – a combination of primarily ON and OFF bipolar cell input with smaller contributions from the inner retina and photoreceptors.[46,54] This is why the mf-ERG is clinically used for a range of ocular conditions, from diseases affecting the bipolar cells (e.g. autoimmune retinopathy and congenital stationary night blindness) to damage to the inner retina (e.g. glaucoma), and conditions that show overlapping levels of damage (e.g. diabetes). A plausible mechanism for a mf-ERG deficit in migraine is peripheral vascular insufficiency manifesting in the retinal blood supply (possibly indicative of a more gener-

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alized vascular dysregulation in people with migraine, as reviewed previously in Ref. 55), which could affect any level of the retina and optic nerve. Our mf-ERG results, taken together with those of Verroiopoulos et al.,[42] suggest that the neuronal origin of localized visual deficits in people with migraine is unlikely to be cortical and therefore unrelated to the pathophysiology of migraine itself.

To our knowledge, only one other study has recorded the mf-ERG in people with migraine,[42] finding a significant reduction in the mean retinal response density only at the fovea relative to control participants. Note that the amplitudes reported by Verroiopoulos et al.[42] were larger than ours across all eccentricities (e.g. 4-fold greater amplitudes of 200 nV/deg^2 and above at the fovea) and therefore not directly comparable here. In contrast, we recorded approximately 50 nV/deg^2 foveal mf-ERG amplitudes, consistent with values previously reported in other studies using similar mf-ERG methods to ours.[56–58] This discrepancy in absolute mf-ERG amplitude values may partly be due to our use of Dawson-Trick-Litzkow thread electrodes (10% smaller ERG amplitudes compared to gold-foil electrodes[59]) or a liquid crystal display (25% smaller ERG amplitudes compared to a cathode ray tube monitor[60]) for stimulus presentation. Regardless of the raw mf-ERG amplitudes, it is not clear from the previous study by Verroiopoulos et al.[42] why foveal function would only be affected by migraine. There is scant evidence for structural macular deficits in migraine (foveal whole retinal thicknesses are not different in people with migraine, for an example, see Ref. 42; see also review in Ref. 55); however, there are increasing reports of OCT angiography of the macular region point to some kind of vascular insufficiency (e.g. enlarged foveal avascular zone)[44] of yet-to-be determined origin.

In contrast, we found mf-ERG deficits parafoveally but not foveally in people with migraine, which is more consistent with the localized interictal visual field losses often detected using 24-2 visual field testing in people with migraine.[4–6,9,10,13] This eccentricity dependence of non-foveal mf-ERG responses in people with migraine has not been noted before, and we can only speculate about the reason for a specific parafoveal deficit. Whereas the mf-ERG is generated in response to localized patterned stimulation across the visual field, the retinotopic structure-function correlation is typically poor for conditions with multiple levels of damage given the multifactorial sources of mf-ERG (e.g. localized mf-ERG deficits do not spatially correspond to visual field defects in people with glaucoma[61–63]). Nevertheless, it may be that retinal vascular dysregulation in some people with migraine creates an environment of neural stress in the retina, leading to susceptibility in the parafoveal area. As our study is cross-sectional, like all other previous studies of migraine, it is not possible to disentangle whether the observed difference in the parafoveal mf-ERG response is a result of specific retinal vascular insult to that area, or a systemic vascular dysfunction that predisposes to retinal vascular alterations that manifest most prominently in that area.

Recent observations may shed some light on this matter. Using a "vessel flux index" on OCT angiography, a decrease in parafoveal retinal perfusion was observed *during* a migraine attack relative to the interictal period.[64] In other case reports, structural OCT and OCT angiography have demonstrated a focal area of parafoveal hyper-reflectivity corresponding to presumed interrupted blood flow, diagnosed as paracentral acute middle maculopathy as a result of presumed retinal vasospasm in individuals with frequent migraine episodes.[65,66] It may be that retinal vascular insufficiency happens with some migraine attacks (indeed, one report has captured transient focal retinal vasospasm associated with migraine[67]), and that one abnormal event could lead to a more permanent localized dysfunction, which becomes evident with clinical electrophysiological and/or visual field testing. Episodic migraine is typically spontaneous, with heterogenous triggers. Although no one in this study voluntarily reported a headache or migraine episode in close proximity to the test visit, a limitation of our study is that we did not formally check when each participant's next migraine attack occurred, relative to our test session. Therefore, for a given individual, it is not possible to know the exact timing of parafoveal mf-ERG deficits within the interictal period. Nevertheless, we did not find a relationship between days post-migraine and mf-ERG response amplitude (our study was not a priori powered to do so). It would be of future interest to track mf-ERG deficits relative to a migraine attack, with more careful characterization of each individual's migraine cycle with a headache diary, to determine if the abnormalities fluctuate with migraine events (suggesting reversibility, similar to how visual field defects are known to fluctuate relative to duration post-migraine[13]) or remain constant over time.

This study was a priori designed to consider both the left and right eyes separately, rather than pooling data from the two eyes as the single previous study of mf-ERG in migraine has done.[42] Therefore, our statistical analysis treated eye as an independent factor in the linear mixed effects modeling. Whereas the International Society for Clinical Electrophysiology of Vision (ISCEV) standard for mf-ERG suggest that "time can be saved by recording from both eyes simultaneously" (Hoffman et al.,[45] p11), we chose to conduct mf-ERG recordings monocularly to be consistent with our visual field testing, with the same opaque patch used to cover the eye not being tested. We found systematically smaller mf-ERG amplitudes and corresponding delayed peak times for the left eyes compared to the right eyes. Visual field sensitivity was also relatively reduced in the left eyes, which may be due to changes in attention/fatigue, or slight adaptation differences after being in the relative dark.[68] This systematic bias is likely a result of our consistent test order (the right eye before the left eye), and an important methodological point to consider in designing, analyzing, and interpreting data when patching is alternated between two eyes. Kondo and colleagues[69] have previously demonstrated an increase in mf-ERG amplitude during the course of approximately 15 minutes of ambient light exposure. This has been attributed to light adaptation, similar to that observed with full field flash-ERG[70] (i.e. cone photoreceptor re-depolarization and simultaneous release of rod photoreceptoral inhibition promoting cone ERG growth). We assume that our participants' left eyes experienced shorter light adaptation periods after being patched, and therefore showed reduced mf-ERG amplitudes and delayed mf-ERG peak times. Despite smaller amplitudes in the left eyes, the overall group statistical results remained consistent across the two eyes and demonstrates the ability of standard mf-ERG to detect a moderate effect size (Cohen's *d* of difference between migraine versus control ring 2 mf-ERG amplitudes = 0.64).

In conclusion, we found abnormally reduced mf-ERG responses parafoveally in people who have no frank visual field loss and are otherwise healthy and asymptomatic in

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between migraine attacks. This suggests a potential retinal locus of neuronal dysfunction in people with migraine, and adds further complexity to diagnosing and tracking progression of co-morbid ocular conditions that may present with mf-ERG deficits, such as glaucoma.[46,62,71,72]

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