Contrast-Processing Dysfunction in both Magnocellular and Parvocellular Pathways in Migraineurs with or without Aura

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Purpose. To assess contrast-discrimination thresholds in patients with migraine who have manifest visual field loss. This study was undertaken to determine whether contrast processing abnormalities in migraineurs are more readily identified by using stimuli that elicit a response from the subject that depends, at least in part, on adaptation mechanisms, and if so, whether deficits appear more pronounced in magnocellular (M) or parvocellular (P) visual pathways.

Methods. Ten patients with migraine who had abnormal visual fields measured with flicker perimetry but had normal standard automated perimetry (SAP) thresholds participated, along with 15 age-matched control subjects. Contrast-discrimination performance was assessed with the steady-pedestal (magnocellular) and pulsed-pedestal (parvocellular) stimuli of Pokorny and Smith for seven pedestal luminances between 15 and 60 cd/m² on a background of 30 cd/m². Subjects were tested foveally and midperipherally at 12.5°. Migraineurs were tested in the quadrant of worst visual field performance. Control subjects were assessed in locations matched to those of the migraine group.

Results. Foveal performance was not significantly different between the migraine and control groups for either task. At 12.5° the migraine group had significantly raised thresholds for both conditions. Effect size statistics revealed similar deficit magnitudes for each test (steady pedestal, −1.06; pulsed pedestal, −1.04).

Conclusions. Dysfunction in both the M and P pathways was identified in the midperipheral visual field of the migraine group. The P pathway dysfunction was not identified by SAP. These findings support the possibility of nonselective neural adaptation abnormalities in some subjects with migraine. (Invest Ophthalmol Vis Sci. 2003;44:442–448) DOI:10.1167/iovs.02-0630

Migraine is a common neurologic condition affecting 10% to 15% of adults. Many people who experience migraine report associated visual symptoms, most commonly photophobia or mild disturbances such as blur. A subgroup experience more severe symptoms known collectively as a visual aura, thought to arise from a change in cortical neural function known as cortical spreading depression. Because the visual pathways are involved in the pathophysiology of migraine in many individuals, it should not be surprising that a number of investigators have identified visual deficits in migraineurs by using either visual field assessment or alternate methods of assessing contrast processing. Visual field deficits have been identified in 30% to 50% of migraineurs between migraine episodes. This abnormal function does not seem to be the direct result of the effect of visual aura on the cortical visual pathways, because deficits have been reported in subjects who do not experience visual aura, as well as in those who do.

Although homonymous visual field deficits characteristic of cortical involvement have been reported after migraine, most visual field deficits are nonhomonymous and are often unilateral. Several studies exploring low-level spatiotemporal processing in migraine have identified presumptively precortical visual processing anomalies.

There is substantial evidence that visual information is transmitted from the retina to cortical area VI by three pathways that are largely separate anatomically and functionally. These are the parvocellular (P), magnocellular (M), and koniocellular (K) pathways. Cells within these pathways differ in morphology and electrophysiological response properties. These differences have been reviewed extensively elsewhere. Relative to P cells (approximately 80% of ganglion cells), M and K cells are large and sparse. In several diseases, including glaucoma, diabetes, and retinitis pigmentosa, visual dysfunction is detected more readily by tests designed to assess the function of M or K pathways than by those that assess the function of P pathways. Migrainous visual field loss is no exception: More substantial deficits have been identified with either temporal modulation perimetry (hereafter referred to as flicker perimetry), which is designed to assess preferentially the performance of the M pathway, or with short-wave-length automated perimetry (SWAP), than with standard automated perimetry (SAP). SWAP assesses sensitivity to dim blue lights presented on a bright yellow background, which isolates the K pathway.

Two theories have been proposed to explain the performance advantage of visual-function–specific perimetry for detecting glaucomatous visual field loss. These theories may be relevant to precortical visual field loss associated with migraine. The first theory is that damage selectively involves ganglion cells with large axons early in the disease process, presumably because these large fiber cells have a metabolic disadvantage under adverse conditions. The second theory proposes that sparser ganglion cell populations are more likely to manifest functional loss, even in the presence of equivalent proportional loss across all pathways, due to their reduced redundancy. These theories need not be mutually exclusive, and both predict greater measurable loss of functions governed by M and K cells. Recent evidence from experimentally induced glaucoma in primates reports M and P pathways to be similarly involved, lending support to the reduced-redundancy argument in glaucoma. Migraine has been proposed as a vascular risk factor for glaucoma and is recog-
nized as one of the most important risk factors for the progression of visual field loss in normal-tension glaucoma. An intriguing possibility regarding migrainous functional deficits is that they may represent reversible abnormalities in cell function rather than cell loss. We have previously reported data for a subject with unilateral visual field loss measured with flicker perimetry that gradually recovered after migraine over a period of 35 days. Similarly, Drummond and Anderson have reported improvements in performance in response to kinetic perimetry during the first 7 days after migraine.

How best to identify psychophysically the cells that are malfunctioning has not been established and has important implications for possible neuroprotective therapy for eye disease such as glaucoma. One possibility raised from previous work is that malfunctioning cells may demonstrate adaptation abnormalities. We have identified deficits in patients with migraine that were readily identifiable with flickering stimuli presented on a luminance pedestal, although performance was normal in response to stimuli flickering about a mean luminance (counterphase-flickering Gabor patches, such as would produce the frequency doubling illusion). Thresholds measured with luminance pedestal flicker differ from those measured with mean modulated flicker, due both to local light adaptation and interactions between the spot and its surround. There is some evidence for adaptational anomalies in early glaucoma, and alterations in metabolism in both M and P neurons have been demonstrated in primates with experimentally induced glaucoma. Sick cells may have altered adaptational states, so that adaptation occurs more slowly or incompletely, or so that light and dark adaptation are affected differentially. If so, early functional loss should be more readily detectable using methods in which performance is dependent, at least in part, on retinal adaptation mechanisms. Such strategies may provide a more sensitive test for P pathway dysfunction.

In this study, we explored M and P pathway contrast processing by using a contrast-discrimination task in a group of patients with migraine who demonstrated visual field loss when tested with luminance pedestal flicker (Medmont M700; Medmont Pty, Ltd., Camberwell, Victoria, Australia) but not with standard automated perimetry (hence, these subjects demonstrate apparently M pathway selective visual field loss). We used the steady- and pulsed-pedestal contrast-discrimination methods of Pokorny and Smith which have been used to explore M- and P-pathway sensitivity in retinitis pigmentosa. These tasks briefly present luminance increments on luminance pedestals. With the steady-pedestal stimulus, the subject must make a contrast-discrimination judgment after adapting to the pedestal luminance, whereas with the pulsed pedestal, the subject adapts to the background. The adaptational, contrast gain, and temporal summation properties of the steady- and pulsed-pedestal tasks differ and have been shown to be consistent with those of the M and P pathways respectively. We assessed migraineurs foveally and peripherally in an area of visual field loss to determine whether contrast-discrimination deficits appear selective for the M pathways, or whether P-pathway dysfunction occurs in the absence of dysfunction measurable by SAP. We were also interested in whether the deficit magnitude identified in either pathway differs with level of retinal adaptation.

**Methods**

Fifteen nonmigraine control subjects (aged 25 ± 4 years) and 10 migraineurs (aged 27 ± 6 years) participated. Subjects were approximately but not exactly age-matched. They were required to meet the following visual and ocular health criteria: best corrected visual acuity of 0.75/5 or better, refractive errors less than ±5.00 D sphere and ±2.00 D astigmatism, normal anterior eye and ophthalmoscopic examination, no evidence of glaucoma, and no history of diabetes or other systemic disease known to affect ocular function with the exception of migraine. No medications known to affect visual field sensitivity or contrast sensitivity were allowed. None of the subjects with migraine showed optic nerve disease consistent with glaucoma, and all had intraocular pressure of less than 21 mm Hg. Migraineurs were tested at a minimum of 4 days after migraine offset to enable washout of medication taken to relieve migraine symptoms and were not permitted to take prophylactic abortive migraine pharmacotherapy. Migraineurs were required to have migraine symptoms that meet the International Headache Society’s criteria7 for either migraine with aura (MA) or migraine without aura (MO). All subjects provided written informed consent in accordance with a protocol approved by the University of Western Australia’s Human Research Ethics Committee and in agreement with the tenets of the Declaration of Helsinki.

The 10 migraineurs were recruited from a cohort of 40 migraineurs participating in an ongoing study of visual performance in patients with migraine. As part of the larger study, visual fields had been assessed with SAP and flicker-perimetry (model M700; Medmont Pty Ltd.). A detailed description of the perimeter can be found elsewhere. In brief, the perimeter uses a zippy estimation of sequential testing (ZEST) thresholding procedure. Flicker thresholds were determined with the autoflicker test, which is described elsewhere. The test patterns for the SAP and flicker test differed slightly and are shown in Figure 1. Test stimuli were arranged in concentric rings. Thresholds were collected from the 3°, 6°, 10°, 15°, 22°, and 30° rings for SAP (Fig. 1A) and the 1°, 3°, 6°, 10°, 15°, and 22° rings for the flicker test (Fig. 1B). Migraineurs who demonstrated a visual field deficit on flicker perimetry were invited to participate. One of the subjects also manifested a deficit in SAP testing. For the purposes of this study, a visual field deficit was defined as three adjacent abnormal points at P < 0.05 or two adjacent points with one abnormal at P < 0.01, on either the age-normal plot (similar to the total-deviation plot produced by the Humphrey Field Analyzer [HFA]; Humphrey Instruments, San Leandro, CA) or hill-of-vision plot (similar to the pattern deviation plot of the HFA). These plots are shown in Figure 1 for a representative subject in the migraine group. Points adjacent to the blind spot were excluded from analysis. This criterion has been used elsewhere for classification of visual field deficits associated with neuro-ophthalmic disorders.

The criterion used to classify visual field deficits for entry into the study was based on the internal normative database of the perimeter. We also wanted to compare the perimetric thresholds between our groups directly and therefore determined mean sensitivity in each subject for regions corresponding to those tested subsequently with the contrast-discrimination paradigm. These regions are illustrated by squares superimposed on Figure 1, left. For SAP, central sensitivity was determined by averaging sensitivities in the eight locations measured in the innermost ring (3°, shown as the central square in Fig. 1A). For flicker perimetry, the four locations in the central 1° ring (shown as the central square in Fig. 1B) were averaged. Peripheral sensitivity for each test was obtained by averaging four locations (two on the 10° and two on the 15° ring) straddling the diagonal meridian in the quadrant tested. These locations were identical for SAP and flicker perimetry.

**Contrast-Discrimination Stimulus**

The test stimuli were based on those described by Pokorny and Smith. Stimuli were generated by a program custom-designed in commercial software (MatLab; ver. 6.1; The MathWorks, Natick, MA) running on a Pentium III (Intel Corp., Mountain View, CA), 933-MHz computer that housed a video card (VSG 2/5; Cambridge Research Systems, Kent, UK). The images were displayed on a gamma-corrected color monitor (frame rate, 120 Hz; mean luminance, 38 cd/m²; CIE...
Steady-Pedestal and Pulsed-Pedestal Stimuli

The stimuli and time course of presentation are illustrated in Figure 2. Figure 2A shows the steady-pedestal stimulus, which consists of four squares (the pedestal) presented continuously, within a 30 cd/m² surround. During the test interval, one of the squares is briefly incremented (30 ms) in luminance. The pulsed-pedestal condition is shown in Figure 2B. A small fixation marker is presented continuously within a 30 cd/m² surround. The four squares are presented only during a brief interval (30 ms) with three of the squares having the pedestal luminance, and one square with the pedestal in addition to a luminance increment. For both steady- and pulsed-pedestal conditions, the subject is required to identify the square that incremented in luminance.

Thresholds for pedestals representing both decrements (15, 19, and 24 cd/m²) and increments (38, 47, and 60 cd/m²) from the mean luminance (30 cd/m²) were measured. For foveal testing, each of the four squares were 1° of visual angle separated by 9 minutes of arc (min arc). The black fixation dot was 9 min arc and was presented in the center of the screen. For peripheral testing, the size of the squares and the gap between them was increased to 1.73° and 13 min arc, respectively. Because retinal ganglion cell density decreases with eccentricity from the fovea, an increase in area of the squares was made in an attempt to assess an approximately equal number of ganglion cells foveally and peripherally. Estimates of ganglion cell density as a function of eccentricity were obtained from Curcio and Allen (see Fig. 6 in Ref. 51) which are based on ganglion cell counts of human retinas in subjects of ages similar to those in the current study (i.e., less than 37 years). The ratio of M and P cells also varies with eccentricity; however, we did not scale the stimuli for this factor as well, because the estimated ratio differs only slightly from fovea to 12.5°. Estimates of M-
and P-cell ratios determined according to Wang et al. (see equations 1 and 2 in Ref. 52) predict the percentage of P cells to drop from approximately 95% at the fovea to 93% at 12.5°, and the ratio of M cells to increase from approximately 5% to 7%.

Procedure

All subjects were tested monocularly, both centrally and in a single peripheral location. For the migraineurs, the peripheral location was chosen to be in the quadrant of worst visual field performance. Control subjects were tested in peripheral locations matched to those of the migraine group. Foveal and peripheral measures were obtained in separate test sessions. For each subject all measures were obtained in a single test session of approximately 1.5 hours’ duration.

Subjects adapted to each stimulus condition for 1 minute. For the pulsed-pedestal condition (B), the black fixation dot was presented within the adapting field (30 cd/m²), and, during the test interval, the four-square array was briefly presented (30 ms) with the luminance of one of the squares incrementally increased in intensity relative to the other three.

Effect sizes54 were determined to enable comparison of the magnitude of deficits across the different tasks, which represents the difference between the groups in numbers of standard deviations. Effect size (d) was calculated as

\[ d = \left( \frac{\mu_m - \mu_c}{\sigma_{\text{pooled}}} \right) \]

where

\[ \sigma_{\text{pooled}} = \sqrt{\left[ \frac{1}{2} \left( \sigma_m^2 + \sigma_c^2 \right) \right]} \]

and \( \mu_m \) and \( \mu_c \) are the migraine and control group means, and \( \sigma_m \) and \( \sigma_c \) are the standard deviations.

RESULTS

Visual field sensitivity was compared between the migraine and control groups for the measures made with the flicker perimeter (model M700; Medmont Pty., Ltd.) in the regions of interest represented by the squares in Figure 1. Because similar visual field deficits have been reported in MA and MO groups,5-6,9 data of all subjects in the migraine group were pooled for this and subsequent analysis. The mean ± SE central

![Figure 2](image.png)

**Figure 2.** Contrast-discrimination stimuli. (A) In the steady-pedestal condition, a black fixation dot was presented at the center of the continuously displayed array of four squares. During the test interval (30 ms) the luminance of one of the squares was incremented. For the pulsed-pedestal condition (B), the black fixation dot was presented within the adapting field (30 cd/m²), and, during the test interval, the four-square array was briefly presented (30 ms) with the luminance of one of the squares incrementally increased in intensity relative to the other three.

![Figure 3](image.png)

**Figure 3.** Location of the stimulus for peripheral testing. The four-square test stimulus was presented on the diagonal meridians within in a single quadrant (chosen to be the quadrant of worst visual field performance for the subject with migraine, and matched for the control subjects). Subjects fixated a marker in the center of the screen. Stimuli were placed so that the center of the four squares was 12.5° from fixation.
sensitivity according to SAP was $27.6 \pm 0.6$ dB in the migraine group and $27.1 \pm 0.3$ dB in the control group. Mean ± SE central sensitivity for flicker perimetry was $24.1 \pm 0.6$ dB in the migraine group and $24.9 \pm 0.4$ dB in the control group. There was no significant difference in central sensitivity with either SAP (Mann-Whitney rank sum test, $P = 0.30$) or flicker perimetry ($t_{(25)} = 1.25$, $P = 0.22$).

The mean peripheral sensitivities returned by the perimeter are shown in Figure 4. The mean (± SE) for each subject group is shown along with individual data. Subjects with MA or MO are represented by the filled and unfilled symbols, respectively. There was no significant difference between the mean sensitivity of the groups for SAP ($t$-test, $t_{(25)} = 0.99$, $P = 0.33$), however the median performance of the migraine group was significantly lower than in the control group for the flicker task (Mann-Whitney rank sum test, $P < 0.001$). Effect sizes for the peripheral sensitivities were $-0.42$ for SAP and $-2.43$ for flicker perimetry.

Figure 5 shows the mean ± SE performance of the contrast-discrimination tasks by the migraine and control groups. As expected, the contrast-discrimination functions for the steady- and pulsed-pedestal paradigms differed markedly. When plotted as a function of pedestal luminance, the steady-pedestal stimulus (Fig. 5) resulted in log threshold, increasing approximately linearly with log pedestal luminance. The function was monotonic for pedestals that were either decrements or increments from the background luminance, indicating local adaptation to the pedestal luminance. Linear regression on the steady-pedestal data shown in Figure 5 resulted in slopes of approximately 1.0 as expected for both foveal (95% confidence limits for slope: migraine = 0.9–1.5; control = 1.0–1.4) and peripheral (migraine = 0.9–1.4; control = 0.8–1.5) conditions.

In contrast, the pulsed-pedestal stimulus (Fig. 5) resulted in a V-shaped curve where thresholds increased as the pedestal luminance was either decreased or increased in intensity from the surround. In this case, there was little adaptation to the pedestal; rather, the contrast difference between the pedestal and the background mattered. A curve was fit to the pulsed-pedestal data in Figure 5 using equation 3 from Pokorny and Smith (Reprinted from Pokorny J, Smith VC. Psychophysical signatures associated with magnocellular and parvocellular pathway contrast gain. J Opt Soc Am A. 1997;14:2477–2486.):

$$\Delta C = \frac{K(10/R_{\text{max}})(C_{\text{sat}} + C)^2}{C_{\text{sat}} - (10/R_{\text{max}})(C_{\text{sat}} + C)}$$

where $\Delta C$ is the contrast-discrimination threshold; $R_{\text{max}}$ is the maximal response amplitude; $C_{\text{sat}}$ is the semisaturation constant (the contrast at which the response amplitude is half $R_{\text{max}}$); $C$ is the Weber contrast; and $K$ is a vertical scaling parameter. As in Pokorny and Smith, $C_{\text{sat}}$ was set equal to 1.0; $R_{\text{max}}$ and $K$ were free parameters in the curve fit, and luminance difference rather than $\Delta C$ was plotted in Figure 5. Percentage contrast gain is determined as $(R_{\text{max}}/C_{\text{sat}})\times 100$. $R_{\text{max}}$ was determined from the best fits of equation 3 in Pokorny and Smith to the data in Figure 5 ranged from 18 to 36, which are similar to those measured by Pokorny and Smith for this test stimulus and fall within the range typical of the P pathway.

Data for foveal fixation are shown in Figure 5A. A two-way, repeated-measures ANOVA showed no significant difference between migraine and control groups for either the steady-pedestal ($F_{(1,6)} = 1.13$, $P = 0.29$) or pulsed-pedestal ($F_{(1,5)} = 0.25$, $P = 0.62$) paradigms. Furthermore, no significant interaction was present between subject group thresholds and pedestal luminance ($F_{(1,6)} = 1.22$, $P = 0.30$ for the steady-pedestal condition and $F_{(1,5)} = 0.17$, $P = 0.97$ for the pulsed-pedestal condition).

Data for the peripheral viewing condition are shown in Figure 5B. Both M-pathway (steady pedestal) and P-pathway (pulsed pedestal) thresholds were elevated in the migraine group in comparison with the control group. The differences in group mean performance were significant for both the steady-pedestal (two-way, repeated-measures ANOVA, $F_{(1,6)} = 12.83$, $P = 0.002$) and pulsed-pedestal conditions (two-way, repeated-measures ANOVA, $F_{(1,5)} = 11.95$, $P = 0.002$). No significant interaction was present between subject group thresholds and pedestal luminance ($F_{(1,6)} = 0.95$, $P = 0.48$ for the steady-pedestal condition and $F_{(1,4)} = 2.01$, $P = 0.1$ for the pulsed-pedestal condition).

Effect size calculation found the magnitude of the peripheral deficit in the migraine group to be almost identical for the two tests (steady pedestal, $-1.06$; pulsed pedestal, $-1.04$).
Because there was no significant interaction between the pedestal luminance and the difference between the groups, these effect sizes are the mean of the effect size statistics calculated for each pedestal luminance.

**DISCUSSION**

In agreement with previous reports, this study demonstrates that contrast processing is not normal in some subjects with migraine when tested at times between episodes.\(^5\)\(^-\)\(^12\) Contrast discrimination deficits were demonstrated in the midperipheral visual field, using separate tasks that are thought to measure M and P function.\(^46\) Effect size measures demonstrate that the deficits in function in the two pathways were similar in magnitude. These findings, together with previous work identifying dysfunction of the short-wavelength-sensitive pathways\(^8\) provide evidence for nonselective visual dysfunction in migraine.

Patients with migraine commonly report a dislike of flickering lights, and several studies have identified increased aversive responses in comparison with control subjects when viewing high-contrast grating stimuli.\(^56\)\(^-\)\(^57\) There is a possibility that thresholds were raised in our migraine group because of heightened visual discomfort. Because we found only peripheral loss, this possibility seems unlikely. Peripheral visual dysfunction may be more readily identified than central loss, because ganglion cells are distributed more sparsely and have larger axons in the peripheral visual field.\(^35\)\(^-\)\(^37\) However, we found a similar magnitude of loss in both M and P pathways, even though M cells are larger and more sparsely represented.

Lumiance pedestal flicker has been shown to identify early visual loss in a number of diseases.\(^7\)\(^-\)\(^8\)\(^58\)\(^-\)\(^59\) Anderson and Vingrys\(^45\)\(^-\)\(^48\) have shown that thresholds measured with lumiance pedestal flicker differ from those measured with mean modulated flicker due to both local light adaptation and interactions between the spot and its surround. We had identified presumably M-pathway deficits in migraineurs, by using stimuli that flickered around a pedestal luminance in the presence of largely normal thresholds for stimuli flickering around a mean luminance.\(^8\) Herein we show that dysfunction of the P pathway can also be identified by using stimuli for which performance is governed, in part at least, by neural adaptation mechanisms, in the presence of normal thresholds measured with SAP. Over the range of pedestal luminances assessed, deficits in M and P pathway contrast discrimination in the migraine group were of similar magnitude, regardless of whether the pedestal luminance intensity was an increment or decrement from the intensity of the background. This implies that deficits could be identified by testing at a single pedestal luminance, within the range assessed in this study.

The pathophysiological mechanism underlying migraineous contrast processing abnormalities is unknown. Such deficits may represent temporary cell malfunctioning, although visual field deficits are commonly encountered in young patients with migraine at durations of weeks to months after a migraine episode.\(^7\)\(^-\)\(^9\) The significance of these deficits to long-term ocular health in these individuals is currently unknown. Several studies have identified a higher prevalence of migraine in patients with glaucoma than in the general population.\(^60\)\(^-\)\(^63\) Although this finding has not been universal,\(^64\)\(^-\)\(^65\) Migraine has been proposed as a vascular risk factor for glaucoma, particularly normal-tension glaucoma (NTG)\(^40\) and has recently been identified as one of the most important risk factors for progression of visual field abnormalities in NTG.\(^41\) Identifying the similarities and differences in visual functional deficits between migraine and glaucoma is essential to ensure correct clinical diagnosis and possibly in the future to identify strategies to predict which patients with migraine are likely to experience progression to glaucoma with age and which patients with glaucoma with a history of migraine are more likely to show progression of visual field loss.

**References**

25. Johnson CA, Adams AJ, Casson EJ, Brandt JD. Progression of early glaucomatous visual field loss for blue-on-yellow and standard