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Transient Tritanopia in Migraine: Evidence for a Large-Field Retinal Abnormality in Blue-Yellow Opponent Pathways

Marc S. Tibber and Alex J. Shepherd

Purpose. To determine whether the magnitude of transient tritanopia (TT) differs between migraine and control groups. TT is a retinal phenomenon characterized by a paradoxical reduction in sensitivity to short-wavelength (purple) stimuli after extinction of long-wavelength (yellow) adapting displays. A group difference in the magnitude of TT would provide evidence for a retinal contribution to the S-cone–specific color-processing abnormalities that have been reported in migraine.

Methods. Thirty-two migraineurs and 32 age- and sex-matched control participants were tested with a four-alternative, forced-choice procedure to determine S-cone increment and decrement detection thresholds before and after adaptation to a long-wavelength (yellow) display and a neutral (white) display. Migraine history, migraine triggers, and pattern sensitivity were also assessed.

Results. Both groups' detection thresholds for increment (purple) S-cone stimuli were increased after extinction of the long-wavelength adapting display compared with the neutral display, demonstrating TT. This loss of sensitivity was significantly greater in the migraine group. In contrast, loss of sensitivity to decrement (yellow) S-cone stimuli was less marked and did not differ between the groups. The magnitude of TT correlated positively with indices of pattern sensitivity and susceptibility to visually triggered migraines but not with migraine history.

Conclusions. These results demonstrate that abnormalities in a specific retinal circuit contribute to decreased short-wavelength sensitivity after adaptation in migraine. As thresholds did not correlate with indices of migraine history, it is unlikely that this finding reflects cumulative damage induced by repeated migraine episodes. (*Invest Ophthalmol Vis Sci.* 2006; 47:5125–5131) DOI:10.1167/iovs.06-0393

There is ample evidence that visual perception is altered both during a migraine episode and in the interictal phase. Visual symptoms (e.g., photophobia and visual aura (VA)[1]) may be associated with the headache, and visual patterns may cause discomfort between episodes[2,3] or even trigger a migraine.[4,5] Psychophysical, electrophysiological, and functional imaging studies undertaken between migraine episodes suggest cortical processing abnormalities in primary and possibly secondary visual areas.[6–9] There is also psychophysical evidence of precortical visual abnormalities in migraine,[10–12] and several studies, in which various forms of perimetry were used, have highlighted the existence of unilateral or nonhomonymous (and hence precortical) visual field losses.[13–18] Techniques have been used that assess visual fields generally (standard achromatic perimetry) as well as those that assess the magnocellular (frequency doubling perimetry) and short-wavelength (S-cone) pathways (short wavelength automated perimetry [SWAP]). In contrast, a recent study by Harle and Evans[19] failed to find significant differences in the extent of visual field loss between migraine and control groups. Thus, the evidence for significant retinal dysfunction in migraine is conflicting, although in each study the trend has been toward impaired performance in migraine.

Several of the studies that have reported deficits using SWAP have attributed them to nonspecific retinal lesions induced by migraine-related vasospastic events.[14,17,18] Results from more complex psychophysical paradigms have provided evidence for S-cone specific color-processing abnormalities in migraine for which the locus of dysfunction is less clear. Individuals with migraine performed worse than a control group at threshold detection, suprathreshold scaling, and visual search involving S-cone targets.[20–22] Statistically significant differences were found between groups, even when test stimuli were large (occupying 6° of the visual field [VF]) or when results were averaged across the VF (subtending 14° to 22°). Further, the S-cone deficits reported were not indiscriminate, but were restricted to specific target and background color combinations, pointing to the existence of a more complex and widespread dysfunction than isolated retinal lesions and one that could arise from any stage in the visual pathways that retains cone opponency (e.g., the retina, retinofugal projections or primary visual cortex).[23,24]

In an attempt to localize the large-field S-cone selective deficits in migraine within the cone–opponent pathways of the visual system, the transient tritanopia (TT) paradigm was used. TT refers to a paradoxical reduction in sensitivity to short-wavelength (purple) stimuli after extinction of long-wavelength (yellow) adapting displays. Psychophysical[25] and electrophysiological evidence from rhesus monkeys and humans[26–28] have localized TT to a site in the retina downstream from the photoreceptors but proximal to the bipolar cell layer (see the Discussion section). This makes TT an ideal experimental paradigm to determine whether there is a retinal component to large-field color processing abnormalities in migraine.[20–22] Receptoral damage should elevate all thresholds in migraine, before and after adaptation, whereas an abnormality in retinal S-cone pathways should produce differences between migraine and control groups only in the magnitude of TT. If, however, the color-processing abnormalities originate at a site beyond the retina (e.g., within the retinofugal projections or cortex itself), there should be no difference between the magnitude of TT in migraine and control groups. In addition, all threshold data were correlated with several clinical parameters (e.g., migraine history) as well as a measure of pattern sensitivity (illusions experienced in response to visual stimuli[2])

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TABLE 1. Participant Details

Group	Total Observers	Female:Male Ratio	Age Range (y)	Age (y)	Migraine Frequency	Migraine Duration
Control	32	3:1	19–49	30.5 ± 9	—	—
Migraine	32	3:1	20–50	30.4 ± 9	12.5 ± 11	15.3 ± 9
MO	20	5.7:1	20–50	28.5 ± 8	13.4 ± 13	13.2 ± 8
VA	12	1.4:1	20–47	33.6 ± 9	10.9 ± 9	18.6 ± 9.6

Participant age, migraine frequency (number of episodes per year), and migraine duration (number of years experienced) are presented in the form of group means and standard deviations. Migraine participants fulfilled the IHS (2004) diagnostic criteria for migraine. Control participants did not meet IHS criteria and none had a history of frequent severe headaches. MO, migraine without visual aura; VA, migraine with visual aura.

and susceptibility to visually induced migraine, as these factors correlate with performance on certain visual tasks.[22,29]

METHODS

Participants

Thirty-two migraine and 32 age- and sex-matched control participants were recruited. All completed a questionnaire detailing characteristics of their headaches. All migraine participants fulfilled the International Headache Society (HIS) 2004 diagnostic criteria for migraine, with or without VA[30] (Table 1). Control participants did not meet IHS criteria, and further, none had a history of frequent, severe headaches.

All participants had a visual acuity of at least 20/25 binocularly (with or without optometric correction) and were screened for normal color vision with the Farnsworth-Munsell 100-hue test. No participant had taken acute medication within 48 hours of testing, and none were taking daily medication (e.g., migraine prophylactics, antidepressants, or β-blockers). None had experienced migraine within 48 hours preceding the test or in the 24 hours afterward. Informed written consent was obtained in accordance with the Declaration of Helsinki and approval was obtained from Birkbeck College's School of Psychology ethics committee.

S-Cone Thresholds and TT Index

TT has traditionally been studied using monochromatic light[25,31,32]; nonetheless, a reliable TT response can be demonstrated using CRT-generated stimuli and adapting fields of a broadband source,[33] a finding that was confirmed in a pilot study. Consequently, the experimental procedure outlined by Smithson et al.[33] was followed. Stimuli were presented on a 22-in. calibrated CRT monitor with spatial and temporal resolution of 1024 × 768 pixels and 100 Hz, respectively. All stimuli used lay on a tritan line (a vertical line in Macleod-Boynton [M-B] space[34] running from coordinates 0.643,0.003 to 0.643,0.064) and elicited changes in S-cone signals only.

The stimulus comprised a ring of pseudorandomly positioned circles (average luminance: 39 cd/m^2) surrounding a central fixation point (Fig. 1). The inner and outer diameter subtended 1.9° and 3.7°, respectively, at a viewing distance of 1 meter. Spatial and luminance noise (2.7 cd/m^2) were added to minimize edge artifacts and ensure that luminance differences could not be used as a cue. The ring was presented against a gray background [20 cd/m^2; coordinates 0.645,0.021), producing an average Michelson contrast of 32%.

In a four-alternative, forced-choice procedure the observer was asked to identify which 90° arc segment of the ring differed in color from the other three. The distance in color space between the target and nontarget quadrants was manipulated (saturation increase or decrease) using a two-down, one-up staircase procedure, which tracks a detection success rate of 71%.[35] Individual step sizes corresponded to a vertical distance of approximately 0.0014 in M-B space. Two separate staircases were randomly interwoven: (1) decrementing (yellow targets), (2) incrementing (purple targets). Each block ended after 12 reversals of each staircase. Thresholds were calculated as the mean of the last six reversals, and were expressed as the distance in M-B space between the target and nontarget quadrants.

After 5 minutes of dark adaptation, thresholds were measured under three adaptation conditions in separate blocks: (1) baseline: 2-minute adaptation to a neutral gray display that was identical to the background field (20 cd/m^2; 0.645,0.021); (2) experimental: 2-minute adaptation to a bright yellow display (70 cd/m^2; 0.644,0.006); (3) neutral: 2-minute adaptation to a bright white display (also 70 cd/m^2; 0.645,0.021). The neutral condition was included to distinguish between effects mediated by adaptation to a long-wavelength display from more general effects of adaptation to a bright (but chromatically neutral) display.

For each block, at the end of the initial 2-minute adaptation the screen switched to the background gray display for 400 ms, after which a stimulus was presented for 40 ms in conjunction with an auditory cue (Fig. 1). In block 1, the gray background was displayed until a response was made. This sequence was repeated (without the initial 2-minute adaptation) until both staircases had reached 12 reversals. In blocks 2 and 3, each stimulus presentation was followed by a 310-ms delay during which the background gray was displayed, before returning to the appropriate adapting field (yellow or white). This top-up adaptation period lasted 7.25 seconds from the time that a response was recorded, maintaining the observer in a state of constant adaptation.

The order of trial blocks was controlled: After a practice session, baseline thresholds were assessed first for each participant. Experimental and neutral blocks were then undertaken in counterbalanced order.

Pattern Sensitivity

Pattern sensitivity was ascertained by gauging participants' responses to a series of high-contrast, horizontal square-wave gratings (0.8, 3, 7 and 17 cyc/deg), diameter 7.8° Each stimulus was presented 4 times for 10 seconds. After each presentation, participants were asked to note whether they experienced any illusions involving (1) motion, (2) color, or (3) shape.[2]

Migraine Characteristics

A questionnaire was completed detailing migraine characteristics such as the number of years migraine had been experienced, migraine frequency, and the time since the last attack. In addition, participants completed a trigger inventory that asked whether each potential trigger (flickering light, visual patterns and alternating light and shade) "never", "sometimes," or "commonly" triggered a headache.

RESULTS

For each age group (binned by decade), both the migraine and control groups' mean total error scores for the Farnsworth-Munsell 100-hue test fell within the 95% confidence intervals of a normal population[36] and within the range of scores collected previously from 96 control participants by one of the authors.[21] In addition, total error scores and partial error scores

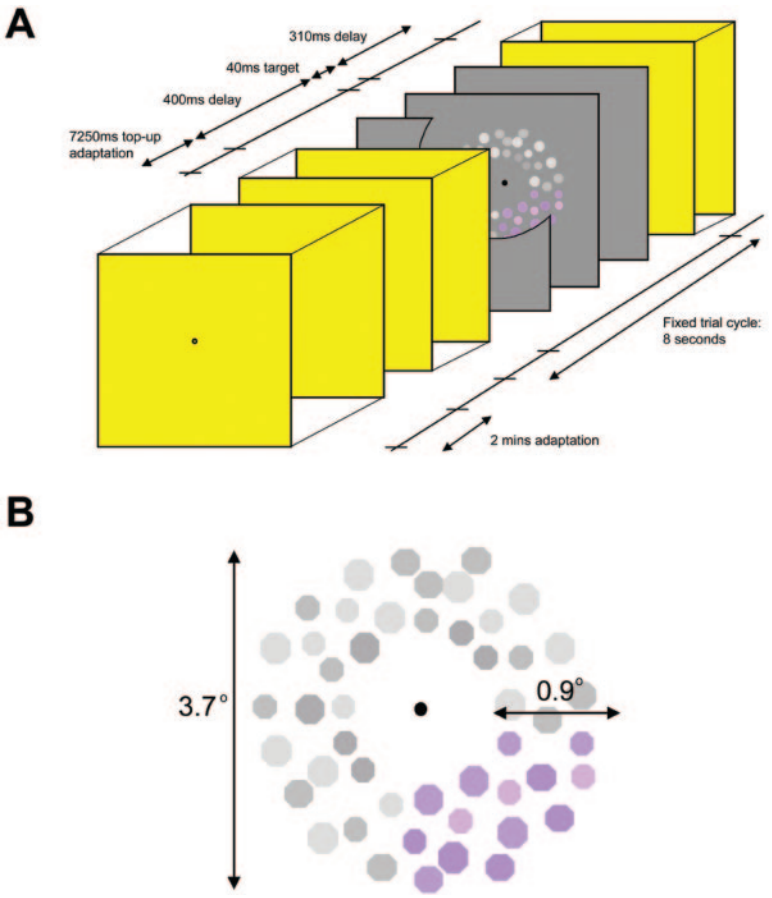

FIGURE 1. Stimulus properties and sequence of events. (**A**) After a 2-minute adaptation, a gray display was presented for 400 ms, followed by a 40-ms stimulus. For the neutral and experimental conditions, each stimulus was followed by a 310-ms delay before returning to the appropriate adapting field for a top-up adaptation period of 7.25 seconds. Adapted with the kind permission of Smithson HE, Sumner P, Mollon JD, eds. How to find a tritan line. *Normal and Defective Colour Vision.* 2003:279–287. © Oxford University Press. (**B**) The task was to identify a 90° arc segment that differed in chromaticity from the other three. The viewing distance was 1 m.

on both the blue–yellow and red–green axes did not differ significantly between the migraine and control groups (each $t_{(62)} < 0.3$, $P > 0.8$; independent samples *t*-test, see Shepherd[21]).

The baseline, neutral, and experimental thresholds for S-cone increments (Fig. 2A) and decrements (Fig. 2B) for each group show three clear trends. First, experimental thresholds were elevated relative to the baseline in each group, for both increment (Fig. 2A) and decrement (Fig. 2B) staircases. In contrast, neutral thresholds were indistinguishable from baseline.

Second, group differences varied as a function of the staircase polarity: experimental thresholds were elevated in the migraine group relative to the control group for increments but not for decrements.

Third, in each condition, sensitivity to S-cone decrements was higher than sensitivity to increments for both groups (each $t > 3$, $P < 0.05$; paired-samples *t*-tests) in agreement with previous reports.[37–40] These statistical comparisons were undertaken after a log transformation of the data, as this renders the increment and decrement threshold distance in M-B color space perceptually comparable.[41,42] Because of these differences in sensitivity, the increment and decrement data were analyzed separately for the subsequent group comparisons.

Increment Thresholds/Purplish Stimuli

The data for the three conditions were normally distributed for each group ($P > 0.2$; Kolmogorov-Smirnov), except for the migraine baseline threshold. This was rectified by the removal of a single outlier. A mixed ANOVA with one between-factor (group: migraine and control), and one within-factor (condition: baseline, neutral, and experimental) was performed. Thresholds were elevated in the experimental condition for both groups tested (Fig. 2A), reflecting TT (main effect of condition: $F_{(1.1,67)} = 310$, $P < 0.001$). Further, the magnitude of this effect was greater in the migraine group (interaction between condition and group: $F_{(1.1,67)} = 4.7$, $P = 0.031$; main effect of group: $F_{(1,61)} = 5.7$, $P = 0.019$). Paired comparisons for each condition revealed that the migraine and control groups differed only for experimental thresholds (independent-samples *t*-tests with Bonferroni correction: $t_{(62)} = 2.5$, $P = 0.015$).

To quantify TT, an increment TTI (TTI_i) was calculated by subtracting the baseline threshold from the experimental threshold for *each* observer (Fig. 3). Thus, the TTI_i represents the relative reduction in sensitivity to short-wavelength light induced by the extinction of a long-wavelength adapting display, a measure that is independent of baseline sensitivity. The TTI_i was significantly elevated in the migraine group relative to the control group (Fig. 3; independent-samples *t*-test: $t_{(31)} = 2.09$, $P = 0.04$).

A second mixed ANOVA was performed on the data from the migraine group alone. The between-factor group was replaced by migraine type (with or without visual aura). There was again a significant effect of condition ($F_{(1.1,32)} = 187.7$, $P < 0.001$), but no significant effects involving migraine type (each $F < 1.3$).

Correlations. In the control group, a positive correlation was found between age and the experimental increment threshold ($r = 0.43$, $P = 0.008$), a correlation that carried through to the TTI_i ($r = 0.47$, $P = 0.003$). In the migraine group, a similar trend was found, although it did not reach statistical significance (experimental: $r = 0.24$, $P = 0.095$; TTI_i: $r = 0.21$, $P = 0.11$). Conversely, there were no significant

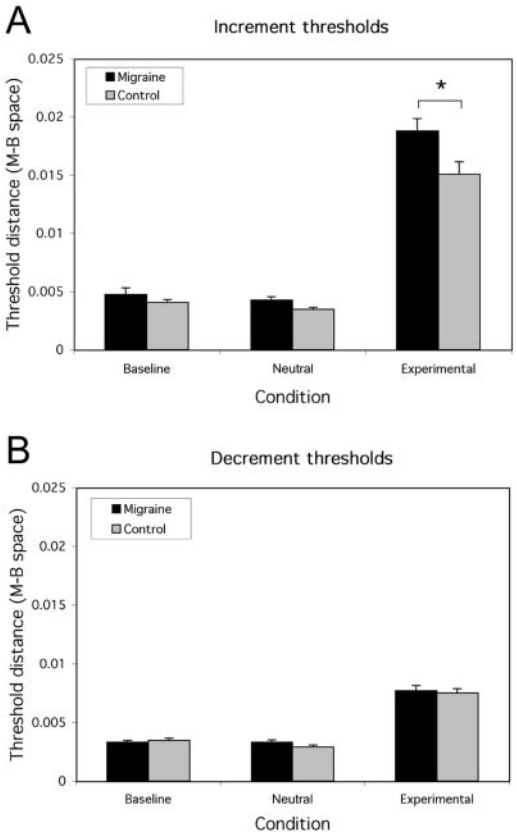

FIGURE 2. Increment and decrement S-cone thresholds. (**A**) Increment S-cone thresholds for migraine (with and without VA pooled) and control participants. Experimental thresholds were elevated relative to the baseline in both groups, reflecting TT. The magnitude of this response was greater in the migraine group. (**B**) Decrement S-cone thresholds in the migraine and control groups. Experimental thresholds were elevated relative to baseline but did not differ between participant groups. $^*P < 0.05$.

correlations between age and baseline or neutral thresholds in either group (largest, $r = 0.015$, NS). Thus, in a typical population, the TTI_i increases with age. However, this pattern may be masked in the migraine group due to a general elevation of the TTI_i.

No significant correlations were found between any of the thresholds and the number of years that individuals had experienced migraine, migraine frequency, or the time elapsed since the latest episode. Similarly, when the thresholds and TTI_i were ranked, they did not correlate with ranked migraine severity (migraine frequency × number of years experienced). These results suggest that the elevated TT is not a consequence of cumulative damage from migraine episodes, but instead reflects a characteristic difference that is independent of migraine history.

In the control group, the Farnsworth-Munsell partial error scores for the blue–yellow axis correlated positively with the baseline and experimental thresholds ($r = 0.3$, $P = 0.04$ and $r = 0.36$, $P = 0.02$) and the TTI_i ($r = 0.31$, $P = 0.04$). In the migraine group, however, there were no significant correlations between these measures.

Decrement Thresholds/Yellowish Stimuli

The data for the three conditions were normally distributed ($P > 0.1$; Kolmogorov-Smirnov) with the exception of the baseline thresholds from the control group. This was rectified by the removal of a single outlier. The same mixed ANOVA was performed to compare the migraine and control groups' decrement thresholds. This revealed a significant main effect of condition ($F_{(1.3,80)} = 271$, $P < 0.001$), reflecting the slightly elevated experimental thresholds (Fig. 2B), but no significant effects involving group (both $F < 1$). Thus, in contrast to the increment (purplish) thresholds, decrement (yellowish) thresholds did not differ between migraine and control groups. As was the case for the increment stimuli, baseline and neutral thresholds were indistinguishable.

A TTI was also generated for the decrement thresholds (TTI_d): experimental threshold minus baseline threshold (Fig. 3). The TTI_d did not differ between migraine and control groups (independent samples *t*-test: $t_{(21)} = 0.6$, $P = 0.55$). Similarly, migraineurs with and without VA did not differ with respect to any of the decrement thresholds (mixed ANOVA: each $F < 1$).

Correlations. The correlations between age and S-cone decrement thresholds were identical with those described for the increment thresholds: in the control group age correlated significantly with the experimental threshold ($r = 0.38$, $P = 0.02$) and the TTI_d ($r = 0.34$, $P = 0.03$). A similar trend was found in the migraine group, although the correlations did not reach statistical significance ($r < 0.25$, $P > 0.05$). None of the indices of migraine history or severity correlated significantly with the decrement thresholds.

For both the control and migraine groups, the Farnsworth-Munsell partial error scores for the blue–yellow axis did not correlate significantly with any of the thresholds.

Pattern Sensitivity and Visual Triggers

Pattern sensitivity was gauged by recording the number and type of illusions seen in high-contrast, square-wave gratings. Four patterns of differing spatial frequencies (0.8, 3, 7, and 17 cyc/deg) were presented, and each participant was exposed to the same pattern four times. Scores for each illusion type (color, motion, shape) were consistently higher for the migraine group for each pattern. A general illusion index (GII) was generated, reflecting overall pattern sensitivity. First, the frequency with which color, motion, and shape were seen was determined for each pattern (minimum, zero of four presentations; maximum, four of four). These were then averaged across the patterns and finally summed to give the GII. The GII was significantly larger for the migraine group than for the control group (4.9 compared to 2.4; $t_{(60)} = 4.1$, $P < 0.001$), indicating that the former are more sensitive to pattern-induced illusions.[2,3]

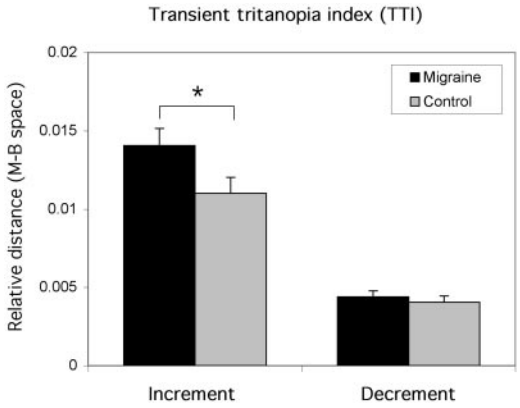

FIGURE 3. The TTI is calculated by subtracting the baseline threshold from the experimental threshold. The increment TTI (TTI_i) was significantly elevated in the migraine group relative to age- and sex-matched control participants. In contrast, the decrement TTI (TTI_d) did not differ between groups. $^*P < 0.05$.

TABLE 2. Rotated Component Matrix

	Component 1	Component 2
Increment baseline	**0.765**	0.089
Increment neutral	**0.630**	0.248
Increment experimental	0.439	**0.607**
Decrement baseline	**0.767**	0.012
Decrement neutral	**0.688**	0.046
Decrement experimental	**0.827**	0.048
Visual trigger score	0.085	**0.710**
General illusion index	0.087	**0.745**

A principal components analysis was undertaken to examine the pattern of intercorrelations between the data. The TTI_i and TTI_d were not included because they are linear transformations of the baseline and experimental thresholds. The correlations between each variable and the factor with which it correlates most highly are shown in bold. Component 1 (a general color component) accounted for 37% of the variance in the original variables, whereas component 2 (the pattern sensitivity component) accounted for a further 19%. The increment experimental thresholds loaded on each component but were more strongly associated with pattern sensitivity than with the other color thresholds.

To determine sensitivity to visually triggered headaches or migraines, all participants were asked to note whether certain visual stimuli commonly, occasionally, or never cause a headache or migraine (in the control and migraine group). Commonly was scored as 2; occasionally as 1; and never as 0 for the following visual stimuli: flickering lights, certain visual patterns (e.g., stripes or lattices), and alternate light and shade. An overall visual trigger score was calculated by summing responses to each trigger for each participant. This was substantially larger in the migraine group than in the control group (1.6 compared with 0.1; $t_{(60)} = 4.6$, $P < 0.001$). Thus, in addition to pattern-induced visual illusions, individuals with migraine are more susceptible to visually triggered headaches.

To explore the intercorrelations between these measures and the experimental data, a principal-components analysis was conducted. Preliminary tests indicated that the data were suitable (Kaiser-Meyer-Olkin measure and Bartlett test). Only two components were extracted with eigenvalues greater than 1. The rotated solution (varimax rotation) led to an interpretation of the two components as (1) a general color-sensitivity component and (2) a pattern-sensitivity component (Table 2).

The increment experimental threshold (i.e., that which reveals TT) correlated reasonably with the general color component, but more highly with the pattern-sensitivity component. All loadings were positive; hence, those people who reported more visual triggers also experienced more illusions when viewing high-contrast gratings and had the highest thresholds when the yellow adapting light was extinguished. These individuals tended to be those with migraine.

Some of these data have previously been published in abstract form.[43]

DISCUSSION

Both migraine and control groups exhibited TT (i.e., sensitivity to S-cone stimuli was reduced after extinction of a long-wavelength adapting display) In contrast, the bright but chromatically neutral adapting display had no effect on thresholds, demonstrating that TT depends on the chromaticity of the adapting field.[25] The TT magnitude differed between the groups for increment stimuli only. Because decrement conditions are rarely included in studies of TT, the increment group differences will be considered first. Possible explanations for the distinct pattern of group differences for increments and decrements will be addressed toward the end of the discussion.

No differences between the migraine groups with and without visual aura were found. Similar performance from participants with and without visual aura has been reported previously[3,10,11,13,15,29,44,45] and led to the suggestion that studies that report differences between the migraine subgroups may have recruited participants for whom migraine classification covaries with other factors, such as pattern sensitivity or susceptibility to visually triggered migraine.[29] The association between the TTI_i, pattern sensitivity and visual triggers reported here is consistent with this suggestion.

Considerable progress has been made elucidating the underlying circuitry of the increment TT (TT_i). Evidence from electrophysiological studies of rhesus monkey and human eyes[26–28] suggest that TT_i is rooted in the outer retina, between the photoreceptor and bipolar cell layers. This is consistent with a model by Augenstein and Pugh,[46] who proposed that S-cone sensitivity is regulated at two sites; the first site representing the photoreceptor itself, the second reflecting a cone-opponent site. The second site involves L- and M-cone feedback on the S-cone terminals, mediated via GABAergic horizontal (Hz) cells. The S-cones' state of hyperpolarization is therefore dependent on the amount of GABA released, which in turn modifies their sensitivity to short-wavelength light. Glutamate is also integral to this circuit as Hz cell activity is driven by glutamate release from the L- and M-cones.

A second component to the model of TT_i incorporates a restorative force that attempts to maintain the system within its optimum operating range, i.e., neither polarized toward yellow nor blue.[37,46] When a yellow adapting display is extinguished the restorative force continues to act and, no longer opposed by input from the L- / M- cones, pushes the opponent site sufficiently toward the blue to produce threshold elevation for short-wavelength light. Regarding the underlying circuitry, the extinction of a yellow adapting field produces a rebound depolarization of the L- and M-cones and their connecting Hz cells which in turn causes a saturation of the S-cones' response through GABAergic hyperpolarization of the membrane potential.[28]

How might an elevated TTI_i relate to abnormalities that have been proposed in the cortex in migraine? As the retina and cortex are ontogenetically connected, the TTI_i has been used as a tool to make inferences about neurotransmitter changes in both neurological and pharmacological studies.[47–49] An elevated TTI_i in migraine is consistent with increased inhibition of the S-cones by Hz-cell mediated L- and M-cone inputs. This could reflect (1) elevated glutamatergic activity at the L- and M-cone/Hz cell synapse, or (2) elevated GABAergic activity at the Hz-cell/S-cone synapse.[48,49] Note also that (2) could occur either independently, or as a downstream consequence of (1). Of interest, there are reports that glutamate levels are elevated both during a migraine attack and in the interictal phase[50–52] while elevated levels of GABA has only been reported during an attack.[53–55]

A common model of cortical function in migraine is one of cortical hyperexcitability, which has been attributed to damage to GABAergic neurons resulting in a lack of cortical inhibition[6,56–58] or to elevated glutamate.[52] In contrast, several psychophysical, electrophysiological, and TMS studies are consistent with elevated levels of cortical inhibition or reduced excitation in migraine.[7–9,29,59] Perhaps general models of abnormal excitation or inhibition are less pertinent in the context of particular experimental paradigms, where the specific circuitry underlying the driven neural response can be identified. Thus, the data reported here are consistent with either increased GABAergic inhibition, or increased GABAergic inhibition *and* glutaminergic excitation, at different sites of a partic-

ular circuit. Previous conflicting models of migraine involving hyper- versus hypo-excitability or increased versus decreased inhibition [6–8,29,52,56–60] may therefore reflect differences in the circuitry that is sequestered by each particular experimental paradigm.

The results of this study also contribute to the understanding of the large-field short-wavelength selective color processing abnormalities that have previously been described in migraine.[20–22] In those studies, it was not possible to identify where in the visual pathways the differences arose, other than ruling out the photoreceptors themselves: if the S-cones were directly affected in migraine, all S-cone thresholds should have been elevated irrespective of background color. Instead, elevated thresholds were restricted to targets on a purple background. This condition mimics the state created after a rebound depolarization during TT, when the system becomes maximally polarized toward the purple and sensitivity declines.[37] Thus, the results of the present study are consistent with the earlier threshold study, and both provide evidence for changes in an early retinal circuit within the S-cone pathways in migraine. It is unclear why deficits are specific to this pathway, although it has been suggested that it is inherently sensitive to physical and chemical damage.[61–63] Alternatively, dysfunction may be detected in this pathway because it is relatively uncommon.[64]

Finally, why is the increment TTI elevated in migraine, while the decrement TTI did not differ between groups? There are two possible explanations: (1) it may merely be an artifact caused by a relatively weak TT effect on S-cone decrements,[37] which masks subtle group differences; (2) it may reflect anatomically distinct retinal circuits that are differentially affected in migraine. Indeed, evidence from psychophysical,[37–39,65] physiological and anatomical[66–68] studies all suggest that S-cone increments and decrements are carried in distinct retinal pathways (S-ON and S-OFF respectively) with different patterns of excitatory and inhibitory input.[66,68] It is, therefore, possible that the S-ON circuitry is particularly vulnerable to damage or abnormal development in migraine.

In conclusion, although dysfunction may exist at multiple sites along the cortical and subcortical color pathways of the visual system in migraine, the present results strongly indicate a retinal contribution. Further, it is unlikely that this is a result of the cumulative effect of migraine-induced damage. A probable explanation is an abnormal ratio of glutamatergic to GABAergic signaling in specific circuits of the outer retina. A disruption in the balance of glutamatergic excitation and GABAergic inhibition has also been described in the cortex in migraine,[52,57] potentially reflecting a common pathophysiology between the two tissues. This putative link is reinforced by the principal components analysis, which demonstrates that the magnitude of TT— originating in the circuitry of the outer retina—is correlated with pattern sensitivity, a measure that reflects activity primarily in the striate cortex.[2]

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