

Thresholds for detection of a target against a background grating suggest visual dysfunction in migraine with aura but not migraine without aura

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Square-wave gratings with particular spatial characteristics induce visual illusions. Patients with migraine are particularly susceptible to these illusions and report discomfort. Their discomfort tends to be greater when the gratings are illuminated by red light, a tendency not shown by controls. Gratings that induce illusions have been found to impair the recognition of optically superimposed targets in headache-free control subjects. We measured the impairment of target detection under illuminants of various chromaticities in migraineurs with and without aura and in matched controls. Migraineurs with aura had significantly higher thresholds for target detection than either migraineurs without aura or controls; in addition, the effect of chromaticity was slightly more pronounced in both migraine groups than in the control group. These findings are consistent with a recent suggestion that migraine with aura might give rise to subclinical damage to the primary visual cortex. □ *Cortical inhibition, migraine with aura, psychophysics, square-wave gratings*

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The grating pattern shown in Fig. 1 consists of alternating black and white bars of equal width. The brightness of this grating, measured along a line perpendicular to the bars of the grating, varies according to a square waveform; the grating is therefore said to have a *square-wave luminance profile*. In addition, brightness is at its maximum for 50% of each cycle of the grating (i.e. for each pair of black and white bars); the grating therefore has a *duty cycle of 50%*. The number of cycles (pairs of black and white bars) of the grating per degree of visual angle

is known as the *fundamental spatial frequency* of the grating.

It has been demonstrated that gratings with fundamental spatial frequencies of about 3 cycles per degree can be uncomfortable to look at, inducing illusions of colour, form and motion (1). The origin of the discomfort and illusions is far from clear, although it has been proposed that the illusions reflect a failure of cortical inhibitory function manifest in response to massive excitatory input (1, 2). Chronicle and colleagues (3, 4) have demonstrated that the square-wave grating patterns which are most likely to induce visual illusions also have psychophysically observable effects on perception. They superimposed a letter target on a variety of grating backgrounds, such that, for each experimental stimulus, the grating did not mask the range of spatial frequencies which are known to be necessary and sufficient for letter identification (5). According to the spatial-frequency channels approach to vision (6), therefore, the letter should have been equally perceptible regardless of the nature of the grating background. Results showed, however, that perception of the target was most impaired when the background grating had spatial characteristics optimal for the induction of visual illusions: it was most difficult when the background grating was of midrange spatial frequency (i.e. approximately 3 cycles per degree) and 50% duty cycle. Furthermore, the difficulty of perceiving the target letter increased

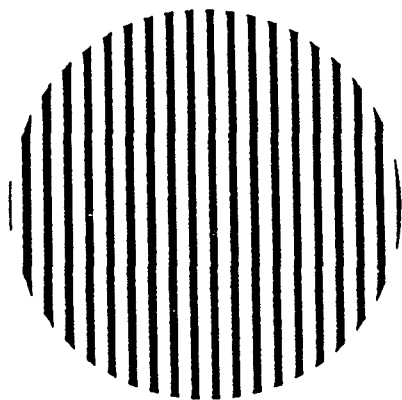


Fig. 1. A high-contrast grating with square-wave luminance profile, 50% duty cycle, and a fundamental spatial frequency of about 3 cycles per degree of visual angle (viewed at a normal reading distance).

linearly with the area of primary visual cortex to which the grating projected.

The primary visual cortex is thought to undergo considerable physiological change during the aura phase of a migraine attack (7). The immediate consequences of this change are the extraordinary visual hallucinations of the typical migraine aura. It has recently been argued that regional cerebral blood flow (rCBF) in posterior brain regions may reach ischaemic levels during the aura phase (8, 9); this argument is supported by high-resolution SPET imaging, which suggests that statistically significant rCBF reductions during migraine aura are confined to the primary visual cortex (10). Chronicle and Mulleners (11) have suggested that the degree of ischaemia in migraine aura may be sufficient to cause permanent, ultrastructural damage to GABA-ergic inhibitory neurons in the primary visual cortex. It might be expected, therefore, that grating-induced effects—both illusions and disruption of target detection—would be more severe in patients with aura, as compared to those without aura, or controls.

Three previous studies have examined grating-induced illusions in patients reporting symptoms consistent with a diagnosis of migraine. Wilkins et al. (1) found that patients who suffered from unilateral headache were more likely to report asymmetric illusions in a 4 cycles/degree grating pattern, although there was no relationship between the side of illusions and the side of the head pain. Marcus and Soso (12) measured visual discomfort by recording the number of aversive movements (wincing, head-turning, etc.) subjects made when shown an appropriate grating pattern and a control pattern. It was found that patients with migraine were significantly more averse to the gratings than were control subjects. Khalil (13, 14) reported that: (i) overall, patients saw more illusions than control subjects, regardless of the size of the stimulus; (ii) patients experienced more discomfort on viewing the patterns than did controls; (iii) illusions and discomfort were more frequent in those suffering migrainous aura than those without aura; (iv) those with unilateral headache were more likely to have asymmetrical illusions, and (v) those with frequent migraine attacks (≥ 1 per week) tended to see more illusions than those with infrequent attacks (5–10 per year).

Coleston and Kennard (15) added to these findings in three respects: first, by requiring subjects to rate the *intensity* of illusions seen in a grating pattern (rather than simply recording their presence or absence); second, by varying the fundamental spatial frequency of the stimulus grating and observing the effects on reported illusion intensity; and, third, by using patients diagnosed according to the most recent criteria of the International Headache Society (16). At all spatial frequencies, migraineurs, especially

those with aura, reported more intense illusions than did controls.

The results of investigations of grating-induced illusions in migraine are thus broadly consistent with the suggestion made above that patients with aura are affected more severely by gratings than those without aura or controls. With one exception (12) subjects in previous experiments have simply been asked to report or rate their subjective percepts. This method brings with it the risk that results may have been due in part to differences between migraine and control groups in respect of their willingness to report symptoms. Migraineurs, for example, have been reported to be more hypochondriacal than control subjects (17); it is therefore possible that they have a tendency to over-emphasize unusual visual symptoms, especially in the context of a medically-related examination or test procedure. It therefore seemed appropriate to use the target-detection method described by Chronicle et al. (3, 4) to compare migraineurs with controls, as this method does not concern itself with subjective symptoms, but rather the objective presence or absence of a target stimulus. Furthermore, given the hypothesized dependence of performance on the target-detection task on the integrity of intra-cortical inhibition, it was thought that a finding of increased detection thresholds in patients with aura would support a suggestion (11) that migraine with aura may give rise to permanent alterations of visual functioning as a result of neuronal damage in the primary visual cortex.

A subsidiary aim of the present study was to follow up an experiment of Chronicle and Wilkins (18), who developed an apparatus to illuminate a grating pattern such that the colour of the light could be varied without changing luminance (brightness). They found that migraineurs (10 without aura and 5 with aura) reliably chose saturated reddish illuminants to maximize the reported discomfort of a grating pattern, whereas controls chose randomly. Given the finding that red light maximized subjective discomfort—and that grating-induced discomfort and impairment of target detection seem to be related (3, 4)—it was tentatively predicted that red light might also increase target detection thresholds in migraineurs, relative to controls and to other colours of light. The experiment to be reported, therefore, compared the target-detection thresholds of migraineurs with and without aura, and controls, when the background gratings were illuminated with red, blue and neutral lights of equal luminance.

Method

Design

The independent variables of this experiment were the diagnosis of the subject (migraine with aura

[MA], migraine without aura [M] or control [C]) and the chromaticity of the illuminant (red [R], blue [B] or neutral [N]). The dependent measure was the luminance of the target letter at which its orientation (up, down, left and right) was correctly and reliably identified. Each subject was presented with each orientation of the target an equal number of times at each chromaticity. The 36 trials were presented in random order.

Subjects

Three groups of twelve subjects took part. One group suffered from migraine with aura (MA: 11 women, 1 man), one from migraine without aura (M: 9 women, 3 men), and the third group were control subjects who did not suffer from migraine headache (C: 11 women, 1 man). Diagnoses of migraine were made according to the criteria set out by the Headache Classification Committee of the International Headache Society (16). The age ranges of patients were MA: 30–69 (mean 47); M: 42–65 (mean 52). Controls were age-matched to the MA patients (range 30–69, mean 47). Chronicity of migraine was matched as closely as possible across the two patient groups (average history 26.7 years [SD 14.4 years] in the MA group and 25.3 years [SD 12.0 years] in the M group). Two subjects in both MA and M groups were taking prophylactic medication for migraine; the remaining migraineurs took medication only during an attack. Migraine subjects were tested inter-ictally. All subjects wore recent refractive corrections appropriate to the task, and none had any colour vision deficiency according to the City University Colour Vision Test (19).

Apparatus

Stimuli were presented in an apparatus, similar to that reported by Wilkins et al. (20), which allowed the chromaticity of the background illumination to be varied. The target was projected into this apparatus using a 35 mm slide projector and filters tinted such that the target and background chromaticities were identical. The voltage applied to the projector lamp was controlled by a thyristor dimmer unit and monitored with an AVOMeter. It was ensured that the chromaticity of the unfiltered lamp did not change appreciably over the range of operating voltages used in the experiment. For each chromaticity condition, the luminance of the target letter measured using a V_λ-corrected spot photometer (Minolta LS-100) was calibrated against the voltage applied to the projector lamp. The calibration was checked at intervals during the experiment.

The target letter was an upper case E, photographed and projected from a transparency. When projected, it subtended 2.2° visual angle horizon-

tally \times 2.2° vertically. The background consisted of a circular grating patch subtending 6° visual angle in diameter, with a fundamental spatial frequency of 3.1 cycles/degree, square-wave luminance profile, 50% duty cycle and space-averaged luminance of 14 cd.m⁻². The grating was mounted on an annulus of grey card of similar space-averaged luminance, 12° visual angle external diameter, such that the bars of the grating were oriented at 45° to the strokes of the target letter. This, in turn, was mounted on the white interior surface of the apparatus (luminance 24 cd.m⁻²).

The chromaticity coordinates (in the CIE 1976 uniform chromaticity scale diagram [21]) for the three illumination conditions were determined on the basis of the findings of Chronicle and Wilkins (18), as follows:

R condition: $u' = 0.361$, $v' = 0.535$. This illuminant appears red. It corresponds to the mean chromaticity of the illuminants chosen by migraineurs to make a grating appear *least* comfortable.

B condition: $u' = 0.171$, $v' = 0.423$. This illuminant appears light blue. It corresponded to the mean chromaticity chosen by migraineurs in a condition where they were asked to manipulate hue and saturation such that the grating appeared *most* comfortable (or *least* uncomfortable).

N condition: $u' = 0.256$, $v' = 0.526$. This neutral illuminant was provided by an unfiltered tungsten lamp.

Procedures

The subjects were shown the appearance of the target letter on the grating background and then undertook four practice trials, one with each orientation of the target letter, using N illumination. The experimenter increased the luminance of the target to a subthreshold level. Subjects were asked to confirm that they could not identify the letter orientation. The experimenter then increased the luminance of the target letter by 1 dB, and subjects were asked whether they could now see the letter. The procedure was repeated until the subject had correctly reported the orientation of the target letter at four successive luminance levels. The threshold luminance of the letter was then taken as the luminance at the first of these four levels.

After the four practice trials, the subjects completed the 36 experimental trials, which proceeded as above except that chromaticity and letter orientation were pseudo-randomly varied across trials for each subject. Approximately 10 sec elapsed after each trial, during which time the luminance of the background did not change, but its chromaticity was altered for the subsequent trial. The randomization of chromaticity across trials for each subject minimized the possibility of systematic adaptation effects. Longer breaks were taken after the 6th, 16th and 26th trials, so that the subjects did not become fatigued.

Results

The voltage readings were converted into \log_{10} (luminance) values, and the mean value of the 12 trials in each chromaticity condition calculated for each subject. Within-subject variability was assessed by examining the standard deviations around these means: they varied between 0.03 and 0.14 log units, with no systematic influence of diagnosis being apparent.

Mean values were then subjected to analysis of variance with diagnosis as the between-groups factor and chromaticity as the within-groups factor. For both F-ratios involving a within-groups factor, the Huynh-Feldt epsilon was in excess of 1; uncorrected probability values were thus used in each case.

There was a significant main effect of diagnosis ($F[2, 33] = 6.94$; $p < 0.01$). Post-hoc pairwise comparisons performed using the Newman-Keuls method demonstrated that the threshold for probe letter detection was significantly ($p < 0.05$) higher for the MA group than for either the M or C groups, but that the M and C groups did not differ significantly.

There was also a main effect of chromaticity: detection threshold was significantly lower in condition B for all groups of subjects ($F[2, 66] = 241.05$; $p < 0.01$).

A significant interaction of diagnosis with chromaticity condition emerged ($F[4, 66] = 3.41$; $p < 0.05$). This interaction is represented in Fig. 2. Further investigation of the interaction effect was undertaken by the use of orthogonal linear contrasts.

Contrast 1 examined the difference between R and N conditions, with respect to diagnosis. There was no effect of diagnosis ($F[2, 33] = 2.39$; n.s.), which demonstrated that the threshold for probe detection

did not differ significantly between chromaticity conditions R and N for any of the three subject groups.

There was, however, a significant effect of diagnosis in Contrast 2, which examined the mean of R and N conditions versus the B condition ($F[2, 33] = 4.03$; $p < 0.05$). The source of this effect was further investigated using the Newman-Keuls method, which demonstrated that the difference between the threshold in condition B and the mean threshold of conditions R & N was significantly ($p < 0.05$) greater for both MA and M subjects, as compared to C subjects.

Discussion

Investigation of the main effect of diagnosis on the threshold for target detection showed that patients suffering migraine with aura had significantly higher thresholds than either the migraine without aura or the control group. The M and C groups did not differ statistically. This result is in partial agreement with previous research examining subjective reports of visual effects given by migraineurs observing square-wave grating patterns with fundamental spatial frequencies in the range 3–4 cycles/degree. Khalil (13, 14) found that patients with aura reported significantly more illusions and greater discomfort than those without aura, and that both migraine groups were affected to a greater extent by the grating than was a control group. On the other hand, Marcus and Soso (12) videotaped aversive behavioural responses to a grating and found no difference between aura and without aura groups. One reason for the disparity between the results presented in the foregoing experiment and those of Marcus and Soso (12) might be that the letter detection task focuses patient attention on the identification of an everyday visual stimulus unconnected with discomfort. It may thus avoid a risk inherent in video-observation methods that patients (regardless of diagnosis) are driven by a desire to impress or the investigator the severity of their complaint and hence purposely exaggerate their responses to stimuli.

The investigation of the interaction between diagnosis and chromaticity condition by analysis of contrasts revealed that both patient groups differed from controls, with respect to the difference between the mean threshold for conditions R and N, and the mean threshold B. In other words, for both migraine groups as compared to the control group, red and neutral illuminants resulted in a greater increase in threshold relative to the threshold with a blue illuminant. Neglecting the N condition for a moment, this result is in accord with the results of Chronicle and Wilkins (18), where a group of subjects heterogeneous as to type of migraine reported maximum discomfort when viewing a grating pattern under very similar reddish illuminant.

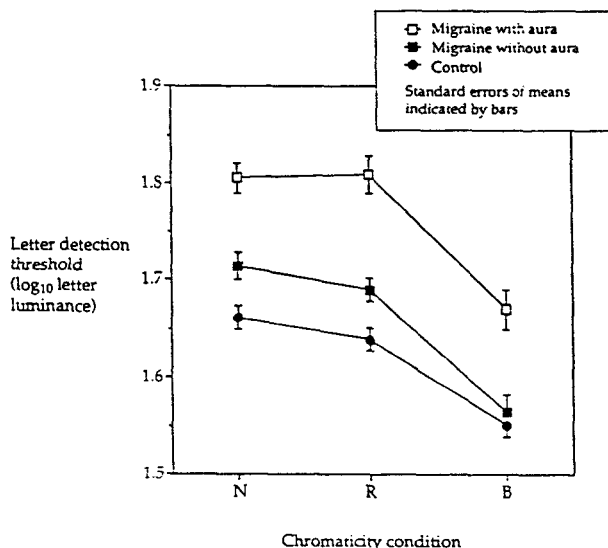


Fig. 2. The interaction of chromaticity condition and diagnosis.

The lack of any significant difference between R and N conditions revealed by Contrast 1 was, however, unexpected. One possible explanation is that the chromaticity coordinates of conditions R and N lay within approximately 3 just-noticeable-differences (jnds) of each other, as compared with the difference between the R and B conditions (~ 6 jnds) or N and B conditions (~ 8 jnds). In effect, the R and N illuminants were perceptually more alike in colour than other pairs of illuminants. It was possible, therefore, that the similarity of mean threshold for letter detection between R and N conditions came about because the chromaticities of the two conditions were insufficiently different.

The main effect of chromaticity was caused by a significant difference in mean threshold values between R and B, and between N and B conditions. There was no significant difference between N and R conditions. The overall reduction in threshold in the B condition may be related to the method used to equate luminances; V_{λ} -corrected photometers can underestimate the luminance of short-wavelength (i.e. blue) stimuli. Perhaps no main effect of chromaticity would have been observed had the background luminances been matched by heterochromatic flicker photometry. Such a procedure was not, however, feasible with the apparatus used.

The effects of changing the colour of the illuminant are difficult to interpret in the context of these methodological difficulties; nevertheless, they do not detract from the clear overall difference in thresholds between the MA group and the other two groups. Although the grating used in the task contained spatial frequencies to which the human visual system is very sensitive at threshold levels, it is unlikely that the pattern of data with respect to diagnosis can be explained by positing higher contrast sensitivity in the MA group: Khalil (13, 14) has shown that the spatial contrast sensitivity function is normal (in migraine without aura) or depressed (in migraine with aura). Rather, we suggest that high thresholds in the letter detection task may be a reflection of disordered inhibition in the primary visual cortex. It has been argued that disordered inhibition, in migraine with aura, is caused by near-ischaemia in the primary visual cortex during the aura phase of each attack (11). It is possible, on the basis of results of experiments using animal models (22, 23), that this degree of ischaemia would act selectively to cause ultrastructural damage to a specific neuronal population: GABA-ergic sparsely spinous stellate cells in lamina IV. These cells form an inhibitory network which is of great importance for maintaining the stimulus specificity of cortical simple cells (24, 25). It might be expected, therefore, that those suffering migraine with aura (but not migraine without aura, wherein the ischaemia does not occur) would experience more illusions, and have higher target de-

tection thresholds, when viewing gratings which are thought to place maximum load on GABA-ergic inhibitory processes (1, 2). This is precisely the pattern of data observed.

It is possible, however, that the raised thresholds in the MA groups are not caused by the disease process, but that inter-ictal visual dysfunction is a component of migraine with aura but not migraine without aura. This possibility seems to us unlikely, however, given the similarity of migraine with and without aura in many other respects (26, 27). It is, furthermore, unlikely that the difference in threshold between MA and M groups is an artefact of differences in length of migraine history, as the two groups were closely comparable in this respect (see Subjects section). Nevertheless, it is necessary to establish experimentally that dysfunction of the visual cortex increases with chronicity of migraine with aura, but not with chronicity of migraine without aura, in order to ascertain whether, as suggested, the physiological disruption of the aura phase is the causal agent responsible for the raised thresholds observed here.

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