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Cortical hyperexcitability in migraine and aversion to patterns

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Abstract

Background: Patients with migraine are averse to certain visual stimuli, such as flicker and striped patterns that evoke paroxysmal EEG activity in patients with photosensitive epilepsy. Migraineurs demonstrate a hyper-responsiveness to such stimuli, and there is debate as to whether the aversion and hyper-responsiveness are due to a hyperexcitability of the cortex similar to that in patients with photosensitive epilepsy. In these patients grating patterns with certain spatial characteristics can be epileptogenic, depending critically on their movement. If the contours of the grating drift continually, the grating is not epileptogenic, but if the contours are static or if their direction is repeatedly and rapidly reversed so as to vibrate, the grating then becomes highly epileptogenic.

Methods: We compared aversion to vibrating, drifting and static gratings in migraineurs and controls. The contrast of each grating was gradually increased, but only until the participant felt discomfort, so as to obtain a contrast threshold for aversion with minimal exposure.

Results: Migraineurs had lower thresholds than the control group, indicating greater aversion. For both groups the threshold was higher (aversion was lower) for static than for both types of moving gratings. The drifting gratings were more aversive than the vibrating gratings when both groups were combined.

Conclusion: The findings suggest that the aversion shown by migraineurs is not attributable to a cortical hyperexcitability similar to that in photosensitive epilepsy.

Keywords

Migraine, hyperexcitability, pattern sensitivity, aversion

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Introduction

Several studies have reviewed the psychophysical, electrophysiological and neuroimaging evidence for the hypothesis that in migraine the cortex is hyperexcitable (1,2). Hyperexcitability has been inferred from an over-response to sensory stimuli; for example, migraineurs show more signs of aversion to achromatic gratings than control groups (3,4). In addition, uncomfortable gratings of this kind make target detection more difficult, particularly for migraineurs (5). Migraineurs have a lower threshold for phosphenes from transcranial magnetic stimulation (TMS) of the occipital cortex (6) though with some inconsistency (7), and visual evoked potentials (VEPs) in migraineurs fail to show the usual habituation to repetitive presentations of stressful stimuli (8).

Patients with migraine are generally averse to visual stimuli that evoke paroxysmal EEG activity in patients with photosensitive epilepsy. Migraineurs demonstrate a hyper-responsiveness to such stimuli, evidenced by abnormally large fMRI BOLD activity (9). The EEG of patients with photosensitive epilepsy has been examined during the observation of horizontal gratings with different types of motion (static, drifting or vibrating) (10). Paroxysmal EEG activity was readily evoked when the horizontal gratings vibrated in a vertical direction, moving at 5–10 deg/s alternately up and down at a frequency of 10–20 Hz. When the gratings drifted towards the centre of gaze at the same velocity, upper field continually downward and lower field

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continually upward, paroxysmal activity rarely occurred, even though fixation stability was maintained. Static gratings were more epileptogenic than drifting gratings but less so than the vibrating gratings. It has been argued that the difference between the vibrating and drifting gratings arose because the vibrating gratings alternately excited different populations of neurons, one tuned to upward direction of motion and the other to downward, thereby synchronising large areas of the visual cortex (10). In contrast, drifting gratings should not have synchronised the activity they evoked because complex cells respond to lines over a range of retinal positions, and the contours pass into and out of overlapping receptive fields. The authors therefore concluded that the differences between the patterns were attributable to the part played by neural synchrony in the induction of the epileptic discharge.

A vulnerability of inhibitory neurons to ischemia has been identified and it has been hypothesised that the reduction in cerebral blood flow during migraine attacks could lead to mild cortical damage in patients with migraine. The damage to the inhibitory neurons could create a hyperexcitable cortex, as seen in patients with epilepsy (11). Furthermore, four anti-epileptic drugs have been shown in double-masked trials to prevent migraine attacks (12). This suggests that the hyper-responsiveness seen in migraineurs may be due to cortical hyperexcitability.

In a recent review Coppola and colleagues concluded that the heightened neural response seen in migraine is not necessarily due to a hyperexcitability as seen in epilepsy, but is instead a reflection of a hyper-responsiveness to sensory stimuli (13). They proposed that the hyper-responsiveness is due to dysrhythmia in the thalamo-cortical system, which affects habituation. The extreme differences in the epileptogenic potential of drifting and vibrating gratings permits a distinction between (i) the visual stimuli that excite the visual cortex and (ii) those that both excite and synchronise neuronal activity and are therefore epileptogenic. If migraine is associated with a hyperexcitable cortex, to the extent that there is a heightened sensitivity to stimuli that produce neural synchrony, and the hyperexcitability is responsible for aversion, then vibrating gratings should be expected to create the most aversion. It would also be reasonable to expect that migraineurs would show an elevated response compared to individuals who are free of migraine.

We examined the extent of aversion to static, drifting and vibrating achromatic gratings in migraineurs and controls by presenting the stimuli at low contrast and increasing the contrast progressively until aversion was first reported. Presentation was then aborted. In this way we were able to measure aversion whilst minimising exposure.

Methods

Participants

This study was approved by the Human Research Participant Committee of York University, Ontario, Canada. Twenty-two males and 58 females from the university were either given credits (as a part of their undergraduate course) or were paid $5 for their time. Snellen acuity assessed monocularly and binocularly, calibrated for a viewing distance of 3.66 m, was at least 6/6. Binocularly, contrast threshold was at least 2.4% (measured using an automated letter identification task using Stimuli^{TM} Version 3.5 (Haag-Streit, Mason, OH). There were no red–green colour deficiencies measured using the Ishihara plates and all participants had a stereo acuity of at least 60 sec.arc (Titmus test; Stereo Optical Co. Inc., Chicago, IL).

Participants were asked to fill out a questionnaire regarding their headaches and general health. All those categorised as a 'migraineur' had to fulfil the IHS criteria (IHS2004 G43). Those who did not fulfil the IHS criteria and who reported having fewer than three tension-type headaches per month were categorised as migraine-free controls.

Exclusion criteria

Eight migraine-free individuals who reported a family history of migraine or epilepsy were excluded. Migraineurs with a family history of migraine were included, but none had epilepsy or a family history of epilepsy.

Any participants who admitted 'a significant heart problem' (one control), high blood pressure (none), head or neck injuries (three controls), neurological disease or psychiatric problems (one control), or strabismus, glaucoma or optic neuritis (none) were excluded. Participants who were on any prophylactic migraine medication were excluded (one migraineur), and participants who reported significant recent changes in the frequency of their headaches were also excluded (one control and one migraineur). One migraineur reported experiencing a headache within the previous 12 hours and so their data were also excluded.

Fifteen participants did not satisfy the IHS criteria for migraine and could not be classified as a migraine-free control; their data were excluded. In addition, two controls were excluded for failing to complete the experiment.

As a result of the selection criteria, 2 males and 16 females with migraine (aged 18–49, mean 27.4), and 9 male and 16 female migraine-free controls (aged 18–30, mean 22.1) participated. Of the migraineurs, five were

classified by IHS criteria as having migraine with aura (MA).

Stimuli

Horizontal gratings were created and presented in VPixx Visual Testing Software (VPixx Technologies, Saint-Bruno, QC Canada). All the gratings were achromatic (CCT 4000°K) and had a square-wave luminance profile. Mean luminance of the screen was 54 cd/m^2, and the contrast of the gratings was calculated as: $(L_{max} - L_{min})/(L_{max} + L_{min})$. The gratings filled the entire screen (18.1 × 13 degrees) and had a spatial frequency of 2 cycles per degree (cpd) at the viewing distance of 1.14 m. The stimuli were viewed binocularly in a dark room. Vibrating and drifting gratings moved vertically with a contour velocity of 5 deg/s (10 Hz), and to prevent optokinetic nystagmus, they moved symmetrically either side of a horizontal midline. The profile of motion for the vibrating grating was a triangle wave: the grating drifted vertically at a constant velocity of 5 deg/s either up or down through one half-spatial cycle before abruptly reversing direction.

Throughout the trials, the display contained a central red saltire fixation cross 0.5 degrees high. A uniform grey field was displayed at the beginning of each trial for 15 s to reduce the motion after-effect between trials.

Procedure

To obtain an aversion threshold for each participant with each grating type, the contrast of the grating was increased in steps until the grating was reported uncomfortable to look at and the trial terminated. Participants were asked to look at the central fixation cross throughout the trial. At the beginning of every trial, the grey screen was displayed for 15 s, before the grating appeared at a contrast of 10%, increasing in steps of 10% every 5 s, until reaching a contrast of 80% and thereafter in steps of 5%. Participants were told to indicate when (or if) the contrast of the grating was too uncomfortable to look at by pressing a key, terminating the trial. The stimuli were presented in two blocks. Each block consisted of three repetitions of each type of grating (drifting, vibrating and static), presented in a random order. After a brief break, the block was repeated, resulting in 18 trials in total. The per cent contrast when the participant chose to abort the trial was averaged across all six trials for each grating type.

The aversion thresholds obtained for each individual and each type of grating were analysed using mixed and repeated-measures analyses of variance.

Results

The mean contrast of the grating at which participants chose to abort the trial (aversion threshold) is shown in Table 1 separately for static, drifting and vibrating gratings, and for each group. High aversion to the grating is indicated by a low contrast threshold.

A 3 × 2 mixed analysis of variance was conducted with type of grating (static, drifting or vibrating) and participant group (migraine or migraine-free control) as main effects. There was a main effect of group ($F(1, 41) = 4.74$, $p = 0.035$) indicating that the migraineurs had lower aversion thresholds than the control group; and a main effect of type of grating ($F(1.25, 51.28) = 70.53$, $p < 0.001$), but there was no significant interaction ($F(1.25, 51.28) = 1.54$, $p = 0.224$), indicating that both groups showed similar relative aversion to the three types of patterns.

Separate repeated-measures analyses of variance with type of grating as a factor were conducted for migraine and control groups. For both groups there was a main effect of the grating type ($F(2, 48) = 28.871$, $p < 0.001$ control group; $F(2, 34) = 44.221$, $p < 0.001$ migraine group). For the control group three Bonferroni post hoc comparison (Dunn-Šidák) (14) tests showed that compared to the static gratings, aversion was significantly greater for both the vibrating ($p < 0.001$) and the drifting gratings ($p < 0.001$), and the drifting gratings were more aversive than the vibrating gratings ($p = 0.006$). For the migraine group, the Bonferroni comparison (Dunn-Šidák) tests showed once again that compared to the static gratings, aversion was significantly greater for both the vibrating ($p < 0.001$) and the drifting gratings ($p < 0.001$), but there was no significant difference between the aversion to the drifting and the vibrating

Table 1. Mean (standard deviation) per cent contrast of the grating at which the participant chose to abort the trial. The data are shown separately for migraineurs and controls for each type of grating (static, drifting and vibrating)

	Static	Drifting	Vibrating
Control ($N = 25$)	90.69 (15.87)	65.40 (27.26)	70.00 (27.78)
Migraine ($N = 18$)	82.82 (16.27)	49.95 (22.88)	54.03 (24.49)

gratings ($p = 0.217$). When both migraine and control groups were combined, the difference between drifting and vibrating gratings was significant: of the 38 participants who showed a difference in thresholds for the two moving gratings, 27 showed lower aversion thresholds to the drifting grating than the vibrating grating ($p = 0.014$, sign test).

The difference between migraine participants with aura and those without was not examined because there were only five participants with aura.

Discussion

Migraineurs were more averse to the gratings than controls, and the static grating was less aversive than the drifting grating and the vibrating grating for both groups.

A previous study found that in patients with photosensitive epilepsy, drifting gratings were associated with a lower probability of epileptiform EEG activity than static gratings (10). Vibrating gratings were more epileptogenic than both static and drifting gratings even though the velocity of the contour motion was similar to that of the drifting gratings. The large difference in epileptic potential between vibrating and drifting motion was attributed to the neural synchrony produced by the vibrating motion. It was hypothesised that the vibrating gratings stimulated two populations of directionally sensitive neurons alternately, thereby synchronising the activity (10). According to this hypothesis, the natural eye movements during fixation had a similar though less extreme effect on neural synchrony when viewing the static grating. If migraineurs suffer a cortical hyperexcitability similar to that in photosensitive epilepsy, and aversion is the result of this hyperexcitability, one might have anticipated that drifting gratings would be less aversive than static, *and* vibrating gratings more aversive than static. Instead, the drifting gratings were *more* aversive than the static gratings for both groups. Indeed, when both groups were combined, the drifting gratings were the most aversive.

If hyperexcitability of the visual cortex in migraine is unlike that in photosensitive epilepsy, the differences may be those of degree or extent. An epileptic discharge requires synchronised neural activity over a large area of the cortex (15), whereas the aversion in migraine may be the result of a more localised excitation. Although patients with photosensitive epilepsy usually show an aversion to epileptogenic stimuli (16), aversion to drifting gratings in particular has not been tested in patients with epileptic photosensitivity.

The drifting patterns used in the present study may have been particularly aversive because they evoked motion after-effects (MAE), a form of adaptation. Such after-effects are evident after viewing drifting random dot patterns, when migraineurs show MAE that are longer than in matched controls (17,18). The longer MAE cannot readily be attributed to a hyperexcitability because in healthy volunteers with a photoparoxysmal response (PPR), whose visual cortex is clearly hyperexcitable, the MAE is *reduced* rather than prolonged (19). In the present study, each stimulus was presented for an average of 36 s (32 s migraine group and 40 s control group), possibly a sufficient duration for abnormal adaptation to occur. MAE are only one form of adaptation, however. Adaptation to the static and vibrating gratings may also have occurred but have been manifest as a transitory reduction in contrast sensitivity (20). It is therefore currently unclear whether there is a relationship between aversion and adaptation (normal or otherwise).

It has been argued elsewhere that migraineurs show a heightened response to sensory stimulation compared to controls – both in psychophysical tests and in neuroimaging studies – and that this hyper-responsiveness is attributable not to cortical hyperexcitability, but to a thalamo-cortical dysrhythmia which affects the neuronal response to stimuli (13). The lower aversion thresholds in migraineurs would be consistent with such a perspective. Overall, the results are not consistent with the hypothesis of a (widespread) cortical hyperexcitability in migraine.

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