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Color-selective photophobia in ictal vs. interictal migraineurs and in healthy controls

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Abstract

Aversion to light is common among migraineurs undergoing acute attacks. Using psychophysical assessments in episodic migraine patients, we reported that white, blue, amber and red lights exacerbate migraine headache in a significantly larger percentage of patients and to a greater extent compared to green light. This study aimed at determining whether these findings are phase-dependent – namely, manifested exclusively during migraine (ictally) but not in its absence (interictally), or condition-dependent - i.e., expressed uniquely in migraineurs but not in healthy controls. To determine whether the color-preference of migraine-type photophobia is phase- or condition-dependent, we compared the effects of each color of light in each intensity between migraineurs during and in-between attacks and healthy controls. During the ictal and interictal phases, the proportion of migraineurs reporting changes in headache severity when exposed to the different colors of light increased in accordance with elevated light intensities. During the ictal phase, white, blue, amber and red lights exacerbated headaches in ~80% of the patients; however, during the interictal phase light initiated headache in only 16–19%. Notably, green light exacerbated headaches in 40% and triggered headaches in 3% of the patients studied during the ictal and interictal phases, respectively. With one exception (highest red light intensity), no control

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subject reported headache in response to the light stimuli. These findings suggest that color preference is unique to migraineurs - as it was not found in control subjects - and that it is independent of whether or not the patients are in their ictal or interictal phase.

Keywords

headache; pain; lateral geniculate nucleus; visual cortex; temporal cortex; color perception; cone-opponent cells; trigeminal nerve

Introduction

Aversion to light, usually defined as photophobia, is common among migraine patients undergoing acute attacks [7; 16; 18; 22; 31; 42; 51]. Using parameters such as eye soreness, worsening of the headache, susceptibility to visual illusions, and alterations in contrast sensitivity or motion perception, previous studies have shown that aversion to light is greater in migraine patients during the interictal phase compared to control subjects with no history of migraine [4; 15; 34]. These widely accepted observations have been tested using tools such as the migraine photophobia scale [7; 30], visual discomfort score [8; 11; 43], linear pain/discomfort rating scales [15; 34], and induction of headache or aura [5].

Attempting to understand how light exacerbates headache, we reported that (a) vision-impaired migraine patients who can detect light are more sensitive to blue light as their ability to detect the light depends on activation of melanopsin photoreceptors, which are most sensitive to blue light [37]; (b) during a migraine attack, patients with normal eyesight report that white, blue, amber and red lights exacerbate their headache significantly more than green light [36], and (c) a variety of hypothalamic mediated autonomic responses to light (e.g., shortness of breath, light headedness, dizziness), which are both unpleasant and not color selective, occur more frequently in the ictal than interictal phase and more frequently in the interictal phase than in healthy controls [38].

Following the publication of the aforementioned photophobia studies, we have been asked repeatedly to address the following question: Is the color preference phase-dependent, namely, manifested exclusively during migraine but not in its absence, or condition-dependent, i.e., expressed uniquely in migraineurs but not present in healthy controls. In order to address these questions, we compared the effects of the various colors of light on headache pain rating in three groups: (i) migraineurs during the ictal phase; (ii) migraineurs during the interictal phase; and (iii) healthy controls.

Materials and Methods

All study visits took place at Beth Israel Deaconess Medical Center (BIDMC), Boston, MA (September 2010 - June 2017). The BIDMC Committee on Clinical Investigations approved the study and all participants provided written informed consent.

Participants

Patients were recruited from the BIDMC. The study conformed to the Helsinki Accord for experimentation in humans. Eligible for the study were women and men between the ages of 15–85 years old who met the International Classification of Headache Disorders Committee [45] criteria for migraine with or without aura, and attested to wanting to avoid light during attacks as it hurt them. Other inclusion and exclusion criteria have been described elsewhere [36].

Age-matched healthy control participants were recruited through advertisement at BIDMC. They were included in the study if they had no history of migraine or other acute / chronic pain conditions.

Psychophysical studies assessing sensitivity to different colors of light

The study included 69 migraine patients and 17 healthy controls. Of the migraineurs, 44 completed the psychophysical assessments during migraine attack (i.e., ictally; these data were reported in Noseda et al., 2016 [36]) that were untreated, and 59 completed the psychophysical assessments while migraine-free (i.e., interictally).

The ictal phase was defined as a headache that fulfilled all criteria for acute migraine based on the International Headache Society (IHS) classification; the interictal phase was defined as a headache-free and premonitory symptoms free status at the time of testing and at the 72-hr period that preceded the testing time (i.e., a patient had to be headache-free for at least 3 days prior to the interictal visit).

All details of experimental design including order, duration, intensity, exact wavelength, calibration and quantification of photic stimulation, dark periods of inter-stimulus intervals, and headache/pain rating instructions given to participants are described in Noseda et al., 2016 [36]. In the ictal phase, patients were asked to describe any change (worsening or improvement) in their headache intensity. In the interictal phase, patients, as well as healthy controls, were asked to report whether or not these lights triggered a headache or any cranial pain. A camera built in the apparatus allowed the examiner to ensure that participants kept their eyes open (not including blinking) throughout the testing.

Statistical Analysis

All analyses were performed using SPSS version 25 (Statistical Package for the Social Sciences, IBM) and SAS version 9.4 (SAS Institute Inc., 2008). Statistical significance was set at $p < 0.05$. The primary outcome measure was defined as proportion of patients demonstrating change in headache pain. For migraine patients during the ictal phase - it was defined as the proportion of patients demonstrating change between headache pain reported in the dark vs. during exposure to the different light stimuli. For migraine patients during the interictal phase and for healthy controls – it was defined as the proportion of participants demonstrating change between the initial headache-free state to any perception of headache during exposure to the different light stimuli. Any change in headache intensity in response to any change in color or intensity of light was reported if it lasted for the duration of the 30 seconds of exposure to stimulation.

Chi-squared tests were used to compare proportions of (i) migraine patients demonstrating increased headache pain rating (migraineurs during the ictal phase), (ii) patients demonstrating an onset of a new headache (migraineurs during the interictal phase), and (iii) healthy controls demonstrating an onset of a new headache. A Bonferroni correction was used to adjust an initial α of 5% for multiple comparisons.

Psychophysical data of pain ratings were analyzed using Mixed Linear Models (MLM) of the PROC MIXED procedure in SAS 9.4. The power effect was defined as random, assuming an unstructured covariance matrix. A random intercept was defined using a covariance matrix. Restricted maximum likelihood was used to estimate model parameters. Color (white, blue, green, amber, red), color intensity (1, 5, 20, 50, 100 cd*m-2) and their interaction terms were included as fixed effects. The primary outcome measure was proportion of participants experiencing stimulation-induced change in headache pain ratings compared to baseline, defined as pre-existing headache pain in migraineurs during the ictal phase (and no headache in migraineurs during the interictal phase or healthy controls). To test current hypotheses (proportion of patients with pain rating change, compared between the colors within each intensity and collapsing by intensity), contrast analyses were applied with simulation-based multiple tests correction within each MLM to reduce alpha inflation.

RESULTS

Enrolled in the study were 69 migraineurs aged [median (25^{th} – 75^{th} percentile)] 39 (29–49) years, of whom 63 were females (91%). Duration of migraine history was 17 (10–26) years, and duration of migraine attacks was 72 (24–72) hours. Migraine attacks were associated with aura (36%), moderate to severe headache intensity (97%), unilateral location (70%), pulsating quality (77%), nausea or vomiting (83%) and phonophobia (86%). The group of healthy controls consisted of 17 subjects, aged 44 (31–51) years, of whom 10 were females (59%).

Sensitivity to light in the different study groups

Out of 44 migraine patients examined during the ictal phase (Fig. 1, left column), a total of 41 patients (93.2%) reported an increase in headache pain ratings in response to at least one photic stimulus (i.e., any intensity of any color). In comparison, during the interictal phase (Fig. 1, middle column), 26/59 patients (44.1%) reported an onset of a new headache by at least one photic stimulus. In contrast, of the 17 control subjects (Fig. 1, right column), only 1 participant (5.9%) reported an onset of a new headache. Comparing the proportions of (i) patients demonstrating increased headache intensity (migraineurs during ictal phase), (ii) patients demonstrating an onset of a new headache (migraineurs during the interictal phase), and (iii) healthy controls demonstrating an onset of a new headache yielded significant differences between all three proportions. Namely, ictal vs. interictal conditions yielded a difference of 49.1% (95% CI: 31.1 – 63.1%, $\chi^2 = 26.481$, Bonferroni corrected $p<0.0001$); ictal vs. controls yielded a difference of 87.3% (95% CI: 61.33 – 95.24%, $\chi^2 = 41.092$, Bonferroni corrected $p<0.0001$); interictal vs. controls yielded a difference of 38.19% (95% CI: 11.9 – 52.8%, $\chi^2 = 8.292$, Bonferroni corrected $p=0.012$).

A post-hoc χ^2 Goodness-of-Fit power analysis incorporating α of 5% and the aforementioned key proportions of the migraineurs during ictal vs. interictal phases demonstrating headache changes in repose to the photic stimuli (93.2 and 44.1%, respectively) yielded a power (1-β) of 99.9% (effect size w = 0.62; noncentrality parameter λ = 38.02; critical χ^2 = 11.07; df = 5).

Sensitivity to color in the different study groups

To determine whether the color-preference of migraine-type photophobia is phase- or condition-dependent, we compared the effects of each color of light at each intensity in migraine patients during and in-between attacks and healthy controls.

Ictal phase—The proportion of patients reporting changes in headache pain ratings when exposed to the different colors of light increased in accordance with the elevated intensities of light (P<0.01; Fig. 2A). At the highest intensity (100 cd·m^{-2}), nearly 80% of the patients demonstrated an intensification of headache; this was true for all colors except for green light, which affected almost half that proportion of patients.

Interictal phase—The proportion of patients reporting initiation of headache when exposed to the different colors of light during their interictal phase, increased in accordance with the elevated intensities of light (P<0.01; Fig. 2B). At the highest intensity (100 cd·m^{-2}), however, white, blue, amber and red initiated headache in 17, 19, 16, and 19% of the patients, respectively, whereas green initiated headache in only 3% of these patients.

As no interaction was found between the variables ‘color’ and ‘intensity’ (P = 0.603), we concluded that the effect of ‘color’ on proportion of patients demonstrating a new onset headache did not depend on the value of ‘intensity’. Accordingly, the effect that each color of light had on proportion of patients demonstrating new onset headache was examined regardless of ‘intensity’ (i.e. all data per color were pooled). Comparing the proportions of patients with a new onset headache across all intensities between colors indicated that these proportions were comparable in response to white, blue, amber and red (P=0.336); however, a significantly smaller proportion of patients reported a new onset headache in response to green as compared to all the other colors (P=0.002).

Control subjects—As for the control subjects, white, blue, green, and amber induced no headache perception at any intensity. The only case in which a control subject reported perception of headache was in response to highest intensity of red light.

DISCUSSION

This is the first study to evaluate in the same experimental setup responses to different colors of light in the context of headache in migraine patients during the ictal and interictal phases as well as in control subjects. Using subjective psychophysical assessments, we demonstrate that migraine patients are more sensitive to all colors of light during the ictal phase compared to the interictal phase and that control subjects do not experience pain when exposed to different colors of light. Specifically, in the migraine patients, we observed that green light (a) exacerbates migraine headache significantly less than white, blue, amber, or

red lights during the ictal phase, and that (b) compared to all other colors, green light is also significantly less likely to trigger a headache during the interictal phase. In contrast, we found no such selectivity in control subjects. These findings suggest that color preference is unique to migraine patients (as it was not found in control subjects) rather than migraine phase (as it was found in the ictal and interictal phases). Given that color perception is generated in the visual cortex, the findings support the notion that the visual cortex processes colors differently in the brain of migraineurs than in the brain of subjects with no previous history of migraine.

The Visual Cortex and Hypersensitivity

Although sought originally as a potential explanation for the migraine brain predisposition to aura [29], it is also reasonable to suggest that abnormal visual cortical excitability is involved in the generation of what migraine patients perceive as enhanced sensitivity to different colors of light. As shown in multiple studies, abnormal visual cortex excitability could be caused by impaired habituation [1; 10; 14; 40; 47] and neuronal hyperexcitability, hyperreactivity or hyperresponsivity [3; 10; 14; 49; 50]. The notion that these functional abnormalities could also play a role in migraine photophobia has been supported by several studies in which greater visual discomfort [19; 20; 27] and stronger activation signals in the visual cortex [4] were observed.

Color Processing and Photophobia

Normal color processing involves cone photoreceptors, retinal ganglion cells, relay neurons in the lateral geniculate nucleus (LGN), the primary (V1) and secondary (V2) visual cortices, and parts of the inferior temporal lobe (V4). In humans, there are three types of retinal cone photoreceptor cells, each classified based on its peak absorption curve along the different regions of the visible spectrum as short (S), middle (M) or long (L) wavelength. To perceive color correctly, the brain needs to receive (and compare) signals that originate in two different classes of cones located in the same area of the retina. Signals originating in different classes of cones activate cone-opponent retinal ganglion cells whose axons project to the LGN, and relay LGN cells whose axons terminate in the visual cortex. Cone-opponent cells increase their firing rate in response to activation of one cone class and decrease their firing rate in response to activation of a different cone class. Cone-opponent cells that compare L and M activation are classified as red-green cells, and those that compare S and M+L activation are called blue-yellow cells. Red-green and blue-yellow signals arriving in V1 activate double-opponent neurons whose role is to compare color signals they receive from cone-opponent neurons across visual space [9; 32]. As such, V1 double-opponent cells establish the neural basis of color contrast, color constancy, poor spatial resolution of color vision, and overall color encoding [6; 12; 17; 23; 26; 44]. In V1, color encoding cells, which are clustered within blobs [25; 46], project to distinct stripes in V2, that in turn convey color signals to the inferior and posterior inferior temporal cortex, where the human brain can generate the perception of millions of different colors [9]. Accordingly, it is tempting to explain our color photophobia findings using knowledge acquired in recent functional imaging studies in which light effects on the brain were assessed in migraine patients and control subjects [41]. While varying greatly in their stimulus paradigm and assessment methods (employing a variety of dynamic and static visual patterns) these studies

demonstrated different patterns of activation or detected greater activation signals in the lateral geniculate nucleus [13]; the visual cortex [4; 13; 15; 24; 35; 49], and the temporal lobe [2; 21] of migraine patients than in healthy control subjects.

In the current study, a fixed order of light colors was used, since randomization would have necessitated a multifold increase in the number of patients in order to maintain the same power of nearly 100%. When a fixed order of stimuli is used, participants' experiences during the first session may influence the following one; this possibility was not controlled in the current study. However, it must be noted that the most painful and aversive color in the current study, blue, was presented 2nd in the order of stimuli, while the least painful color, green, was presented 3rd, i.e. immediately after blue; accordingly, if any carry-on effects took place, one would expect to that the green light would have been biased to be perceived as more noxious than it was. Therefore, it is improbable that green light was experienced as less noxious due to the applied order of stimuli.

Conclusions

In summary, our conclusions replicate and corroborate prior studies that show that during migraine nearly 90% of the patients are photophobic whereas during the interictal phase only half of the patients report abnormal sensitivity to light, to the extent that it can trigger a new attack [28; 33; 39; 52]. Also confirmatory are the conclusions that even when pain-free, migraineurs are more sensitive to light than control subjects [13; 33; 48]. Far from being confirmatory, however, are the novel descriptions of greater aversion to each of the 4 colors of light in the ictal than the interictal phase (in migraineurs) and the virtual absence of aversion to any color of light in control subjects.

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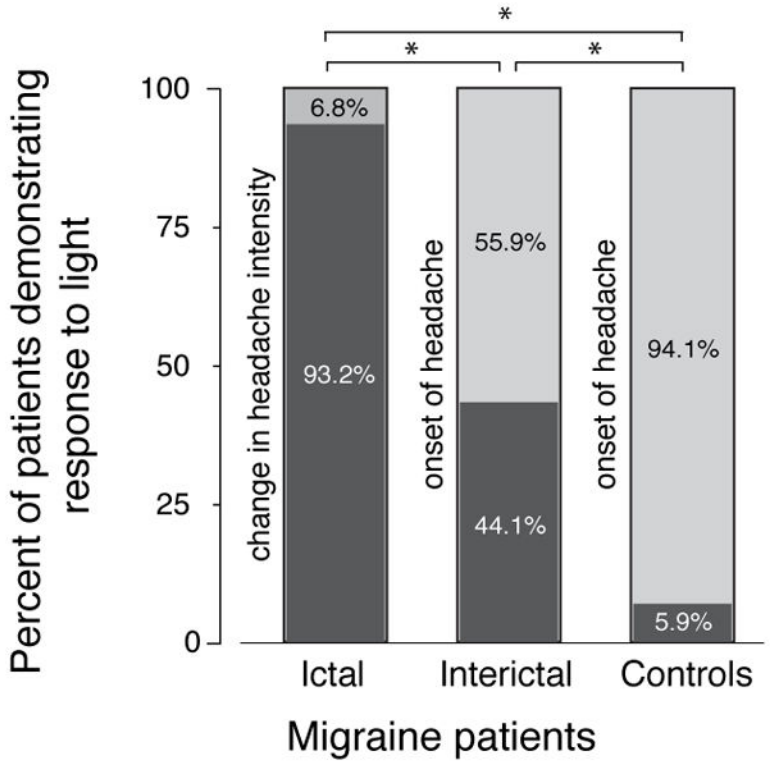

Figure 1.

Proportions of (i) migraineurs during the ictal phase demonstrating increased headache pain rating after the exposure to the photic stimuli as compared to the pre-existing headache (left column, dark grey; N=44); (ii) migraineurs during the interictal phase demonstrating new onset headache after the exposure to the photic stimuli (middle column, dark grey; N=59); and (iii) healthy controls demonstrating new onset headache after the exposure to the photic stimuli (right column, dark grey; N=17). * $P<0.05$.

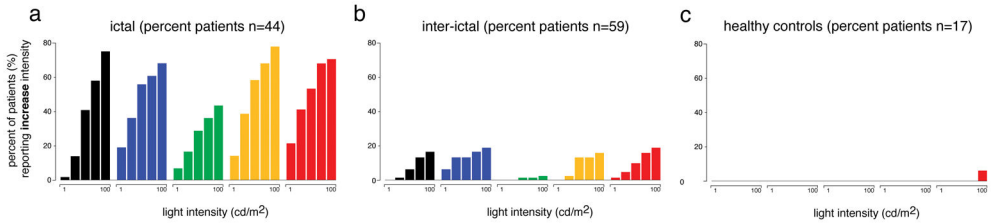

Figure 2.

Proportions of (i) migraineurs during the ictal phase demonstrating increased headache pain rating after the exposure to the various colors of light at the various intensities as compared to the pre-existing headache (a); (ii) migraineurs during the interictal phase demonstrating new onset headache after the exposure to the various colors of light at the various intensities (b); and (iii) healthy control subjects demonstrating new onset headache after the exposure to the various colors of light at the various intensities (c). * $P<0.05$.