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LETTER TO THE EDITOR

Reply: Pupil area and photopigment spectral sensitivity are relevant to study of migraine photophobia

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Sir,

Recently, we reported that green light exacerbates migraine headache significantly less than white, blue, amber or red lights in migraine patients with normal eyesight; that their light-adapted flash electroretinography (ERG) a-wave amplitude is significantly larger in response to blue than all other colours; that their light-adapted flickering ERG a-wave is significantly smaller in response to green than blue and red, and significantly smaller in response to red than blue; and that their P2 visual evoked potential (VEP) wave is smaller in response to green than in response to blue, red or amber lights. Based on the findings, we proposed that cone-driven retinal pathways might be at the origin of this colour-selective migraine-type photophobia (Noseda *et al.*, 2016).

In a Letter to the Editor, Dr Omar Mahroo (2016) raises the possibility that our results were secondary to the effects different colours of light might have on pupil diameter. According to this scenario, a wavelength (colour) that causes the pupil to constrict more will allow less light to reach the retina and consequently will produce less pain, smaller ERG and smaller VEP, and vice versa, a wavelength that causes the pupil to constrict less will allow more light to reach the retina and consequently will produce more pain, larger ERG and larger VEP. If this were the case in our study, one would expect to find smallest pupillary constriction response to blue light, largest to green light and somewhere in between to red and amber lights. In support of this scenario, Dr Mahroo cites a study by Lobato-Rincon *et al.* (2014), which shows that the amplitude and latency of pupil constriction in response to green light is larger than blue and red lights.

The use of pupillometry in the evaluation of photophobia and in the identification of autonomic disturbances in migraine pathophysiology is well established (Micieli *et al.*, 1989; Mylius *et al.*, 2003; Cambron *et al.*, 2014). Pupillometry, however, is based on stimuli that are shorter than 200 ms (as they must be shorter than the latency of the pupillary light reflex; PLR) and as such cannot be compared to the 2.5 min (or 150 000 ms) ambient light conditions used in the psychophysical part of our study. In fact, pupil diameter is readily affected by habituation, fatigue, alertness, information processing load (Tryon, 1975), and other factors that are likely to appear during the prolonged stimuli we used. Given the short duration of the PLR and the pupil habituation factor, the likelihood is low that pupil diameter would have determined what a migraine patient perceives 2.5 min after onset of light stimulus of any colour. In this regard, it is also important to mention that static pupil diameter is significantly smaller in response to blue light (425–445 nm) than green light (515–535 nm) (Bouma, 1962).

Regarding the more likely possibility that pupil diameter affected the magnitude of the ERG and VEP signals, one must take into consideration the fact that the photic stimulus used by Lobato-Rincon *et al.* (2014) was a point light illumination rather than a full-field (Ganzfeld) illumination (used in our study). Our rationale for using the full-field stimulation paradigm was that it represents more closely the daily (ambient) light conditions under which migraine patients develop the perception of photophobia. More importantly however, because light stimuli used in PLR studies differ in intensity and duration (e.g. 200 ms for PLR versus 4 ms for ERG and VEP) from light stimuli used in ERG and VEP studies, it is difficult to interpret the

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Lobato-Rincon *et al.* (2014) findings in the context of ours. In contrast, a brief review of existing literature—where photic stimuli were delivered as full-field (Ganzfeld) rather than a point light source—does not support the scenario that pupil constriction affected our ERG and VEP results. Studying the relative transient and sustained pupil response to red and blue lights in healthy control subjects, Lorenz *et al.*, (2012) reported no significant differences in pupil contraction for stimulation of cones. In agreement with this, Collison *et al.* (2016) compared the magnitude of the light-adapted red and blue ERG waves and the per cent change in transient pupil constriction in healthy control subjects, and as in our study, he found that red light produces smaller ERG (a-wave: 46–94, b-wave: 146–261) than blue light (a-wave: 55–92, b-wave: 168–261) and that the per cent change in pupil size (i.e. constriction) for cones was 37–55% for red and 38–55% for blue (i.e. similar). Collectively, these three studies suggest that chromatic ERG signals are determined mainly by the stimulus wavelength. Nevertheless, we agree with Dr Mahroo's assertion that pupillary diameter must be measured in each such study, as it may provide additional information for interpreting chromatic ERG and VEP signals.

Regarding the part of the study that describes responses of thalamic neurons in the rat, Dr. Mahroo writes:

> The authors were also able, using multi-unit recordings in rats, to identify thalamic neurons responding differently to different wavelengths (least responsive to green light). This is of interest and relevance, but interspecies differences bear consideration. As photopigment spectral sensitivities differ between human and rat...it is not clear that patterns of relative stimulation by different wavelengths will be identical. Thus some degree of caution is advisable before directly relating findings in rodents to the human visual system.

We fully agree with this comment and acknowledge the difficulty in trying to use data obtained in anaesthetized rats to explain a sensory perception in awake patients. Philosophically, we believe that questions, which can be answered in clinical studies (such as the psychophysical assessments, ERG and VEP recordings), should be obtained in human subjects whereas questions that cannot be answered in clinical studies (for ethical reasons associated with risk) should be obtained in animal studies. Following this principle, we believe that our multi-unit recording in the rat provided answers that to a certain extent and with proper caution, could help us unravel the neural substrate of photophobia beyond which we could have done based on clinical studies alone.

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References

Bouma H. Size of the static pupil as a function of wavelength and luminosity of the light incident on the human eye. Nature 1962; 193: 690–1.

Cambron M, Maertens H, Paemeleire K, Crevits L. Autonomic function in migraine patients: ictal and interictal pupillometry. Headache 2014; 54: 655–62.

Collison FT, Park JC, Fishman GA, Stone EM, McAnany JJ. Two-color pupillometry in enhanced S-cone syndrome caused by NR2E3 mutations. Doc Ophthalmol 2016; 132: 157–66.

Lobato-Rincon LL, Cabanillas-Campos Mdel C, Bonnin-Arias C, Chamorro-Gutierrez E, Murciano-Cespedosa A, Sanchez-Ramos Roda C. Pupillary behavior in relation to wavelength and age. Front Hum Neurosci 2014; 8: 221.

Lorenz B, Strohmayr E, Zahn S, Friedburg C, Kramer M, Preising M, et al. Chromatic pupillometry dissects function of the three different light-sensitive retinal cell populations in RPE65 deficiency. Invest Ophthalmol Vis Sci 2012; 53: 5641–52.

Mahroo OA. Pupil area and photopigment spectral sensitivity are relevant to study of migraine photophobia. Brain 2016, in press.

Micieli G, Tassorelli C, Magri M, Sandrini G, Cavallini A, Nappi G. Vegetative imbalance in migraine. A dynamic TV pupillometric evaluation. Funct Neurol 1989; 4: 105–11.

Mylius V, Braune HJ, Schepelmann K. Dysfunction of the pupillary light reflex following migraine headache. Clin Auton Res 2003; 13: 16–21.

Noseda R, Bernstein CA, Nir RR, Lee AJ, Fulton AB, Bertisch SM, et al. Migraine photophobia originating in cone-driven retinal pathways. Brain 2016; 139 (Pt 7): 1971–86.

Tryon WW. Pupillometry: a survey of sources of variation. Psychophysiology 1975; 12: 90–3.