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Intrinsically Photosensitive Retinal Ganglion Cells Targeted Chromatic Pupillometry Using A Ring Light Stimulus

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Abstract **–** With the discovery of the presence of the photopigment melanopsin in the intrinsically retinal ganglion cells (ipRGCs) around 20 years ago, the interest in chromatic pupillometry increased. Melanopsin, and consequently ipRGCs, have a high sensitivity to the blue light, showing a different pupil light response (PLR), especially in the pupil recovery, between the blue and red stimuli. It is also known that, although the ipRGCs are broadly spread in the retina, they do not exist in the fovea, and they are most abundant in the peri-foveal region. Chromatic pupillometry technique normally uses full-field stimulators to deliver the coloured stimuli close to the person's eye. In this study, a novel type of stimuli using a ring light with coloured filters was studied and proposed that could allow a more targeted stimulation of the ipRGCs, reducing the quantity of light entering the retina and maximizing their effect in PLR. This ring light should be placed in a certain distance to the eye, determined with an optical simulation. Some preliminary experiments were made in one individual to assess the viability and potential interest of this type of stimulus. The Post-Illumination Pupil Light Response 6s after the stimuli offsets (PIPR-6s) is a parameter highly used in chromatic pupillometry. The difference of the PIPR-6s value between the blue and the red stimuli was 13.1%, which is aligned with the literature when using full-field stimulators. It was found that, using a ring light as stimuli at 30 cm of distant in the front of the eye, were obtained compatible results as the ones described in the literature. This work indicates a potential new way to stimulate the pupil for chromatic pupillometry, focused on a targeted stimulation of the ipRGCs, that could be used for developing new pupillometer systems more portable and accessible.

Keywords**:** Pupil, Pupillometry, Chromatic pupillometry, Melanopsin, Intrinsically Photosensitive Retinal Ganglion Cells

1. Introduction

Pupillometry is a technique used to assess the Pupil Light Response (PLR) of an individual, either subjectively, by a clinician, or quantitatively, with automated pupillometer. It has been regaining interest over the last two decades since the discovery of melanopsin, a photopigment that was found in the intrinsically photosensitive retinal ganglion cells (ipRGCs) in the inner retina [1], [2]. These cells are characterized by a sensitivity to the absorption of blue light [3], making them the third photosensor of the eye, along with the known cones and rods. Chromatic pupillometry has been growing since then by using blue and red stimuli showing its potential in screening and detecting neuro-ophthalmological diseases. [4]–[6]

In humans, the ipRGCs represent around 0.4-1.5 % of the retinal ganglion cells [7]. Being broadly distributed across the retina, there are no ipRGCs in the region of the fovea and they are most abundant in the perifoveal region [7]. Figure 1 shows a schema of these regions of the macula, providing insights on the perifovea's geometry being as a ring slice.

In chromatic pupillometry with standard commercial pupilometers the colored stimulus are usually generated using a full-field stimulator that is placed close to the eye [8], [9]. Using a stimulator that would allow a more targeted stimulation of the ipRGCs could be advantageous, without the need of being full-field which would mean a different placement in front of the eye, that would be relevant for pupillometry systems with higher portability and easiness of use.

In the present work was studied a novel way to stimulate the ipRGCs using the pupillometry technique, considering a stimulus targeted for the region in the retina where these cells are most abundant. This study involved developing an experimental setup that would allow this goal using a ring light and a standard commercial pupillometer and doing some preliminary validation in healthy individuals.

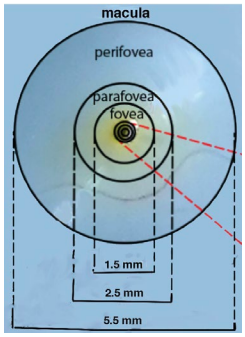

Fig. 1: Human Macular regions [10]

2. Methods

With the intent to build a system that would allow a targeted stimulation of the ipRGCs using chromatic pupillometry, this study had two main parts: estimating the optic characteristics of the system using a simulator; preparation of the experimental setup and the validation of the system on healthy individuals.

2.1. Optic system simulation

For the first section of the work, it was needed to calculate the optimal distance between the ring light stimulator and the eye. This was made using an online open-source optic simulator named *Ray Optics Simulation* [11] that allowed to simulate the human eye optic model and the ideal position of the ring light so that, when the ring light was switched on, it illuminated the retina in the region of the peri-fovea, where the ipRGCs are most abundant.

The Gullstrand eye model was used to simulate the eye in its optical characteristics. In Table 1 are described all the sizes and lens characteristics considered. Some other considerations were made in this simulation to mimic the scenario of the light stimuli switched on and what that would trigger in the eye, to better decide on the distance to use between the ring light stimulus and the eye:

- The ring light we had available had 8.5 cm of diameter;
- It was considered a pupil size of 2 mm, to correspond to the constricted pupil, when the stimulus is ON;
- The light that enters the eye needs to reach the retina in a radius between 1.25 and 2.75 mm from the optic axis.

Table 1: Optical Eye characteristics used in the simulation.

Cornea Power	43D
Cornea focal distance	23mm
Lens Power	4D
Lens focal distance	250mm
Cornea-Lens distance	6 mm
Pupil size	2 mm
Cornea-Pupil distance	2mm
Aqueous humour Refractive Index	1.336
Vitreous humour Refractive Index	1.336

2.2. Experimental Setup

Considering the calculus and simulations described in the sub-section 2.1, it was then implemented a system using available equipments, that would allow real measurements in healthy individuals. For the pupil response recording was used the standard pupillometer PSTxs-II from AMTech GmbH (Germany). This equipment uses a near-infrared camera to record the pupil and its software measures the pupil size in real-time retrieving the pupil size as a function of time. As for the stimuli, a ring light with 8 cm of diameter was used, placed in 30 cm in front of the eye and centred with the pupillometer camera and the individual eyesight. A standard grade cellophane paper, either blue or red, was placed in front of the ring light to filter the light and allow chromatic stimulus. Pupillometric data was exported directly from the pupillometer software and normalized to the baseline (measurements of the initial 5s before the stimulus onset).

The subject's face was supported in a chinrest to guarantee a stabilization of the eye in front of the pupillometer camera.

2.3. System preliminary validation

Preliminary experiments were made in one healthy male individual (34 years old). The acquisition was made in the dark, with the individual head and the ring light - pupillometer setup fully covered with a black cloth to guarantee complete darkness. After 10 minutes of dark adaptation, the recording starts and after 5 seconds (to acquire the baseline pupil size) the ring light switches ON for another 5 seconds and then off continuing recording for another 25 seconds. This protocol was based in Park et al.[8] work, but with a reduction of the stimuli duration to 5s due to the capacity of the ring light used. This experiment was repeated 3 times for each stimulus colour: blue and red. Between each repetition was made a 5-minute pause and between the blue and red full experiments, 10 minutes of pause for the pupil to recover and re-adapt to the dark.

3. Results and Discussion

The optic system simulation allowed to understand at what distance should the ring light be placed so that when it is on the light illuminates the retina in the peri-fovea. Using the *Ray Optics Simulation,* we placed 2 point light sources distances 8.5 cm from each other in relation to the optic axis and move them horizontally until we reached a sensible distance that would have light illuminating the retina in the peri-fovea region. Based on the data from Figure 1 [10], the parafovea has a 2.5 cm diameter and the peri-fovea has a 5.5 cm diameter, which means that the light need to reach between 1.25 to 2.75 cm of radius from the optic axis centre. After some experiments in the simulator, it was found that a 30 cm distance between the eye and the ring light would achieve the desired behaviour, as observed in Fig. 2.

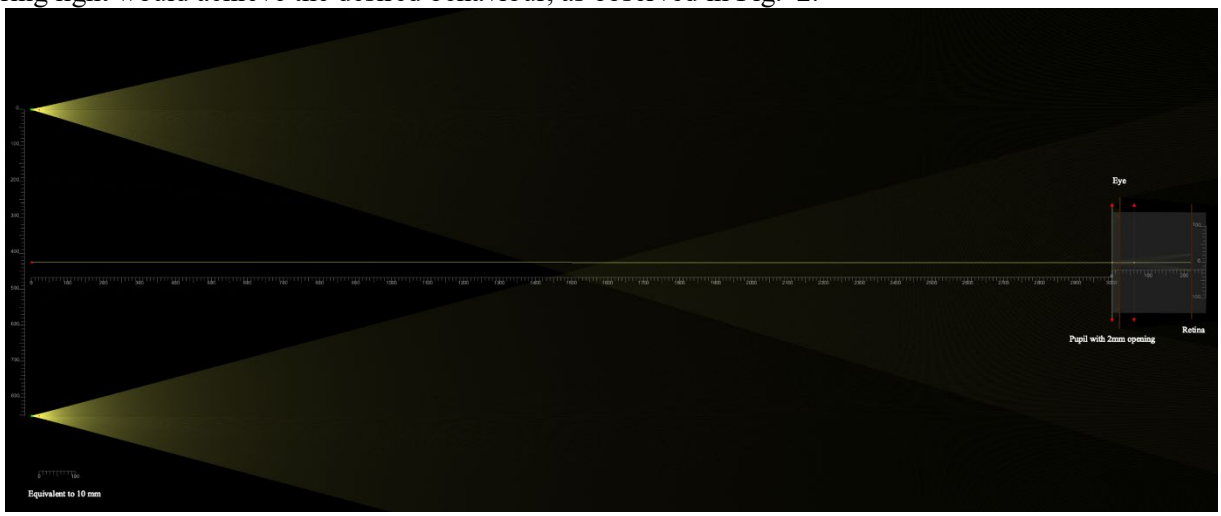

Fig. 2 - Optical simulation with 2 point sources distanced by 8.5 cm to simulate the ring light on the left and the eye model on the right side, with a distance of 30 cm between the ring light and the eye.

The system setup was then implemented accordingly, and PLR measurements were made in an individual for both blue and red stimuli. Fig. 3 shows the results with the pupillometric data acquired, in the average of the three measurements did for each experiment. One can observe that the curves have similar behaviour while the pupil is constricting after the stimulus started (5s) and the pupil recovery was different between the blue and red stimuli, being the blue one slower to recovery after the stimulus offset. During the stimulus it is noticeable that the pupillometer software for pupil detection saturated and

couldn't properly detect the pupil in most of the time the ring light was on, however it is noticeable that the blue stimulus allowed a higher constriction value during the stimulus than the red one.

One parameter usually analysed in the PLR results is the Post-Illumination Pupil Response 6 s after stimulus offset (PIPR-6s), which allows to quantify the difference in the PLR between different experiments. Park et al. [8] presented pupillometric results for healthy individuals for blue and red stimuli with 1 s and 10 s duration. Their results indicated a PIRP-6s difference between the blue and red responses of around 25% for the 1 s duration stimuli and 11% for the 10 s duration stimuli. In our experiment was used a 5 s duration and the PIPR-6s difference between blue and red responses is 13.1%. This value is concordant with the Park et al. [8] results, even though we did not use the same stimuli durations. Another interesting observation is that also in the Park et al. [8] research one observes that the blue stimulus achieves higher constriction values than the red one, which our results also indicate. These preliminary results are then an indicator that this novel approach with a ring light to work as a stimulator targeted for ipRGCs activation has potential. Further experiments are needed to validate this setup and concept on a bigger sample of individuals, healthy and patients with neuro-ophthalmological diseases, in the next step.

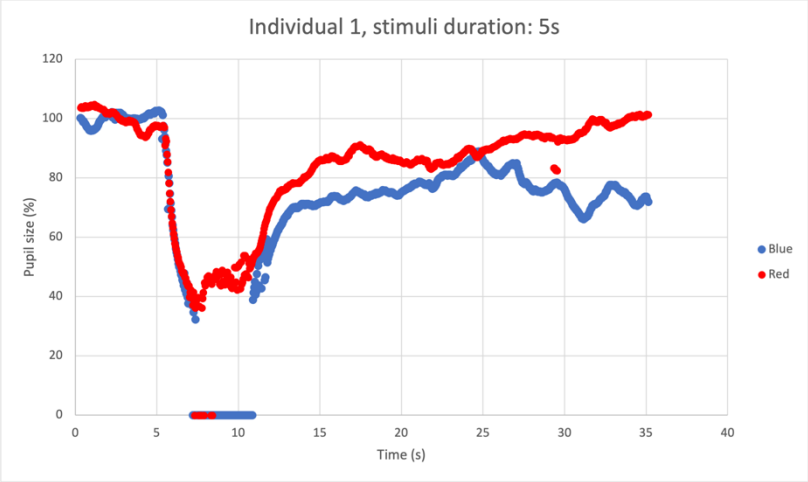

Fig. 3: Pupillometric results for the individual analyzed in this study for both red and blue stimuli (average of 3 measures for each).

4. Conclusion

This work presented a new way to stimulate the ipRGCs based in its location and abundance in the retina for a better and more targeted chromatic pupillometry. Although preliminary and with the experiment being only made in one individual, the ring light shows a potential interest for a stimulus focused in activating the ipRGCs. It also revealed good prospects on being a different option than the full-field stimulators, allowing to be integrated in other type of equipments more portable. Future work should consider experiments in a higher sample of healthy individuals and improvements in the setup for a more steady and replicable system. Further work should also cover experiments in patients with neuro-ophthalmological diseases so that it can potentially used as part of a screening tool.

Acknowledgements

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