Blue Light and Melanopsin Contribution to the Pupil Constriction in the Blind-spot, Parafovea and Periphery

Tim Schilling[1], Mojtaba Soltanlou[2,3], Yeshwanth Seshadri[1], Hans-Christoph Nuerk[2,3] and Hamed Bahmani[1,4,5]

[1]*Dopavision GmbH, Berlin, Germany*
[2]*Department of Psychology, University of Tübingen, Tübingen, Germany*
[3]*LEAD Research Network, University of Tübingen, Tübingen, Germany*
[4]*Max Planck Institute for Biological Cybernetics, Physiology of Cognitive Processes, Tübingen, Germany*
[5]*Bernstein Center for Computational Neuroscience, Tübingen, Germany*

Keywords: Melanopsin, Blind-spot, Optic Disc, Pupil.

Abstract: Retinal photoreceptors modulate the pupil diameter to regulate retinal illumination. At early stage the pupil-response is formed by intrinsically-photosensitive-Retinal-Ganglion-Cells (ipRGCs) expressing melanopsin, activated by blue light. ipRGCs' axons pass through the optic nerve head, corresponding to the blind-spot. No photoreceptors except melanopsin appear to exist in the blind-spot. Contributions of melanopsin to pupil constriction in absence of classical photoreceptors in the blind-spot is not fully understood. We investigated how blue light in the blind-spot changes melanopsin-pupil-response compared to parafovea and periphery. The Post-Illumination-Pupil-Response (PIPR) amplitude reflecting melanopsin was analyzed for standardized time windows (1s<1.7s, 1s>1.8s and 2–6s) and expressed as pupillary-change. Bayesian analysis showed a BF>3 that PIPR>1.8s for blind-spot and periphery is not different. At times 2s–6s, a *t*-test comparison in the blind-spot condition showed a significantly larger PIPR to blue compared to red light, confirming a melanopsin-pupil-response in the blind-spot. Taken together, equivalent stimulation in the blind-spot and periphery revealed comparable PIPR, although there are no rods and cones in the blind-spot. In absence of classical photoreceptors in the blind-spot, melanopsin seems to be responsible for pupil constriction in similar manner as in the periphery, which supports the presence of melanopsin on the axons of ipRGCs.

1 INTRODUCTION

In the human eye, the retina contains a peripheral region without rods and cones where ganglion-cell axons bundle in the optic nerve. The head of the optic nerve is called the optic disc which corresponds to the blind-spot. Although light illumination in the blind-spot is reported to be invisible, but reduces the brightness perception of a white light outside the blind-spot (Saito, Miyamoto, Uchiyama, & Murakami, 2018), this does not mean that the optic disc is insensitive to light.

Melanopsin-expressing retinal ganglion cells (RGCs) are intrinsically photosensitive (ipRGCs) and receive extrinsic input from rods and cones in primates (Dacey et al., 2005; Gamlin et al., 2007). ipRGCs form the afferent pupil pathway to regulate the pupil response (Gamlin et al., 2007).

Pupil size dynamics are controlled by melanopsin containing ipRGCs (Fu et al., 2005; Hattar et al., 2003; Lucas et al., 2003), whose axons pass through the optic disc of the human eye. It has been shown in rats that melanopsin is expressed in cell bodies, dendrites, and proximal axonal segments of this subset of RGCs (Hattar, Liao, Takao, Berson, & Yau, 2002). Melanopsin is sensitive to shorter wavelengths centered around 480 nm (Berson, Dunn, & Takao, 2002; Hattar et al., 2002). In contrast to the short-wave blue spectrum, red light consists of higher wavelengths over 600 nm, which barely overlaps with the sensitivity spectrum of melanopsin.

Light of different wavelengths have been shown to modulate pupil response differently. When the whole retina is stimulated, it has been shown that short-wavelength blue light (467 ± 10 nm) induces a larger change in pupil size, whereas global long-

Schilling, T., Soltanlou, M., Seshadri, Y., Nuerk, H. and Bahmani, H.
Blue Light and Melanopsin Contribution to the Pupil Constriction in the Blind-spot, Parafovea and Periphery.
DOI: 10.5220/0008972404820489
In *Proceedings of the 13th International Joint Conference on Biomedical Engineering Systems and Technologies (BIOSTEC 2020) - Volume 5: HEALTHINF*, pages 482-489
ISBN: 978-989-758-398-8; ISSN: 2184-4305

wavelength red light (640 ± 17 nm) leads to a smaller change (Park et al., 2011).

In the beginning of the 19th century, Hess found a pupil contraction when he focused light on the blind-spot (Hess, 1908). Later, stimuli of different wavelengths were delivered to the blind-spot and the spectral response curve was assumed to be a modified rod curve originating from scattered light (Alpern & Campbell, 1962). Alpern and Campbell speculated on whether the deviation from the rod curve derives from the activity of another photosensitive visual substance in addition to rhodopsin. Their postulated visual substance might be melanopsin, which was shown to be present on ipRGCs' axons a few decades later (Hattar et al., 2002).

Melanopsin-expressing ipRGCs have been documented as playing a role in the pupil light response, contributing to it a sluggish recovery component; an extended response primarily mediated by melanopsin activation that persists for some time after stimulus light termination - referred to as Post-Illumination or Post-Stimulus Pupillary Response (PIPR or PSPR respectively; Münch, Léon, Crippa, & Kawasaki, 2012). There is evidence that melanopsin drives the PIPR, which is a sustained pupil constriction after stimulus offset, produced by the intrinsic response of ipRGCs (Adhikari, Zele, & Feigl, 2015; Dacey et al., 2005; Gamlin et al., 2007). While both rods and ipRGCs have been shown to provide input to the pupil light response, hence rhodopsin and melanopsin contribute largely to PIPR <1.7 s (Adhikari, Feigl, & Zele, 2016), it was reported that melanopsin dominates all phases of PIPR and solely contributes to the PIPR after 1.7 s (Adhikari et al., 2016).

Miyamoto and Murakami studied the effects of light stimulation inside the blind-spot on pupillary light reflex with additional stimulus outside the blind-spot (Miyamoto & Murakami, 2015). A sole stimulation of the blind-spot and its effect on PIPR has not been investigated to date, as far as we know. We conducted experiments to examine the PIPR in the blind-spot as well as periphery and parafovea to have comparable conditions outside the blind-spot. We tested the hypothesis that blue light constricts the pupil more than red light in the blind-spot, when elicited by melanopsin. The purpose of the study was to compare melanopsin-induced PIPR when illuminating the retina with a stimulus a) fitting in the blind-spot and b) of equivalent size on parafovea and periphery.

2 METHODS

2.1 Participants

The study contains data from 15 participants with normal or corrected to normal vision. Visual acuity was assessed before the experiment with FrACT (Bach, 2006) to be greater or equal to 0.0 logMAR.

All experiments were approved by the Ethics Committee for Psychological Research at the Department of Psychology of the University of Tuebingen and conducted in accordance with the tenets of the Declaration of Helsinki. After explaining the experiment, written informed consent was obtained from all participants.

2.2 Stimulus

The stimulus consists of red or blue circular discs presented in three different locations of the retina: in the parafovea, in the peripheral retina and in the blind-spot. The monitor (FUJITSU Display B24-8 TS Pro, Fujitsu Technology Solutions GmbH, Munich, Germany) was placed 50 cm in front of the participant's head, which was stabilized in a chin rest.

The right eye was covered with an eye patch while the left eye dynamics were captured by an eye tracker (EyeLink 1000 Eye Tracking system, SR Research Ltd., Ottawa, Ontario, Canada), after the inbuilt calibration procedure was completed.

The blind-spot of the left eye was mapped using the following calibration procedure: the participant looked at a fixation target and adjusted a disc on the screen within the position and radius of the blind-spot. The fixation target consisted of four points around the center - above, below, left, and right - connected circularly with a thin line (see Fig. 1). The stimulus size and stimulus position had to be adjusted by the participant with a keyboard until the stimulus was invisible for the participant when fixating at all four surrounding fixation points and the centered fixation target. For the parafovea condition the stimulus was in the parafoveal region, meaning outside the fixation target in the horizontal direction towards the corresponding blind-spot, 1.2° inferior and 3.4° lateral leftwards to the fixation resulting in a total distance of 3.4° visual angle from the fixation target. The peripheral stimulus was in the same direction as parafoveal and blind-spot in the visual field, 12.4° distant from the fixation target, located at 4.6° superior and 11.9° lateral leftwards to the fixation target. Stimulus diameter varied among individuals for the blind-spot condition and was 1.25° for parafovea condition and periphery condition.

Blue stimulus was composed of short-wavelength blue light with a peak at 450 nm (CIE color coordinates: x = 0.15, y = 0.06) whereas the red stimulus consisted of long-wavelength red light with a peak at 610 nm (CIE color coordinates: x = 0.65, y = 0.34) stimulus measured with i1 studio (x-rite Incorporated, Kentwood, Michigan, USA) and the software f.luxometer™ LLC (Los Angeles, California, USA). Both stimuli had a luminance of 11.8 cd/m², measured with a luminance meter (Konica Minolta LS-110, Konica Minolta, Inc., Tokyo, Japan). The background of the monitor was set to black. Participants were asked to passively view the fixation target while the stimuli were presented to the target locations. Gaze position was monitored during the experiment to ensure a fixation on the target.

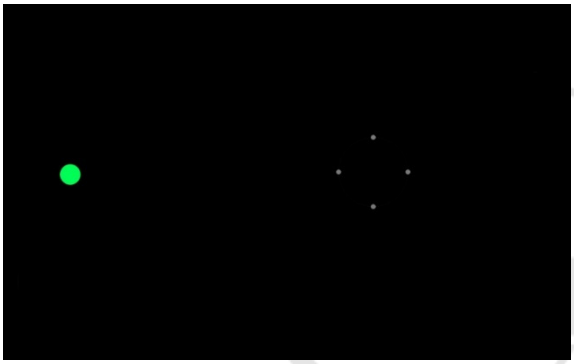

Figure 1: A screenshot of the display during the calibration phase. Stimulus color was green for calibration phase.

The experiment consisted of one block of four trials with two red and blue stimuli, separately (see Fig. 2). The red disc was always shown first to account for the bi-stability factor (Mure et al., 2009). Each block was presented separately for blind-spot condition, parafovea condition, and periphery condition. One block (47.32 s) began with a 23 s baseline, followed by an 80 ms stimulus four times and a 6 s inter-stimulus-interval (ISI). The stimulus length of 80 ms was chosen as it is over the minimal duration for a pupillary light reflex (Webster, 1969) and secondly, to reduce the chance that eye fixation was outside the fixation target.

A 6 s window is recommended when using short pulse (Adhikari et al., 2015).

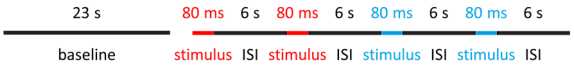

Figure 2: One block consists of a 23 s baseline and an 80 ms stimulus four times followed by a 6 s inter-stimulus-interval (ISI).

2.3 Analysis

Data was preprocessed by down-sampling the signal to 10 Hz, removing blinks and interpolating the signal. Pupil response was corrected to the 500 ms pre-stimulus baseline. Furthermore, the pupillary change was calculated as a percentage relative to the pre-stimulus baseline, as recommended by Kelbsch and colleagues to obtain relative pupil constriction amplitude (Kelbsch et al., 2019). For the Area Under the Curve (AUC) analysis, the pupil response values were calculated to a 100% pre-stimulus baseline, whereas for pupillary change, the baseline was adapted to 0% by subtracting 100%.

The pupillary change was analyzed along different time windows. Following the standards of pupillography, combined rhodopsin and melanopsin contribution was analyzed in a 1 s time window before 1.7 s, and sole melanopsin contribution was analyzed in a 1 s time window after 1.8 s (Kelbsch et al., 2019). Additionally, the AUC from 2 s to 6 s PIPR was calculated, which is until the end of the ISI, which was adapted from the standard AUC of 2 s to 10 s (Kelbsch et al., 2019) because our ISI was not longer than 6 s.

For statistical analysis repeated measure ANOVA for the factor stimulus location and color with post-hoc test Tukey correction was conducted. Additionally, to test the a priori hypothesis, a paired one-sided *t*-test was performed on AUC. Furthermore, Bayesian inference statistics was used in order to test the absence of a difference (null hypothesis). Therefore, the Bayes factors were calculated to evaluate evidence in favor of the null hypothesis (BF_{01}). Bayes factors were categorized to the degrees of evidence by Kass and Raftery (Kass & Raftery, 1995) i.e. BF_{01} = 1-3 is interpreted as weak evidence, BF_{01} = 3-20 is interpreted as positive evidence, BF_{01} = 20-150 is interpreted as strong evidence and BF_{01} > 150 is interpreted as very strong evidence.

For statistical analysis JASP (Version 0.10.2.0, JASP Team, 2019) was used. The rest of the pupil signal processing and preprocessing was done with Octave (John W. Eaton, David Bateman, Søren Hauberg, 2018).

3 RESULTS

We analyzed PIPR for melanopsin contribution in different stimulus locations using three standardized time windows, separately: times < 1.7 s for rhodopsin and melanopsin contribution, and times > 1.8 s for

melanopsin contributions, and 2 s – 6 s for melanopsin contributions, see shaded gray box for different time windows in Fig. 3.

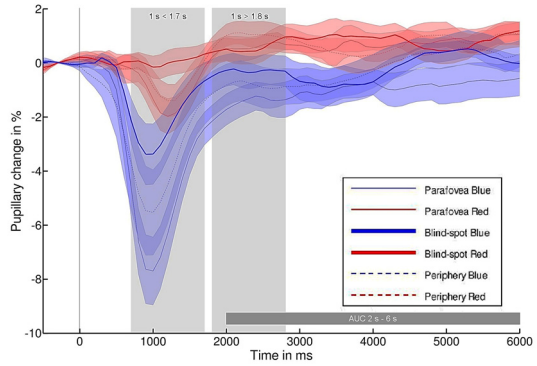

Figure 3: Mean and standard error of the mean (SEM) of pupillary change in % to blue and red stimulus for blind-spot, parafovea and periphery over time in ms. Stimulus onset is at 0 ms.

3.1 Melanopsin and Rhodopsin at Times < 1.7 s

A repeated ANOVA revealed a significant main effect for color ($p < 0.001$) and stimulus location ($p < 0.05$), but not for their interaction ($p = 0.20$), see Table 1.

Table 1: ANOVA of PIPR at times < 1.7 s in detail.

	df	F	p	η^2_p
Stimulus location	2.28	3.60	0.04	0.06
Color	1.14	17.42	< 0.001	0.19
Stimulus location ∗ Color	2.28	1.71	0.20	0.01

Regarding stimulus location, post-hoc tests corrected with Tukey showed that pupil response to the parafovea is larger than blind-spot condition ($p < 0.05$), but no significant difference appeared between the blind-spot condition and periphery condition ($p = 0.25$) and the parafovea condition and periphery condition ($p = 0.50$), see Fig. 4.

Regarding color, post-hoc tests corrected with Tukey showed that pupil response to blue light is significantly larger than the red light condition ($p < 0.001$).

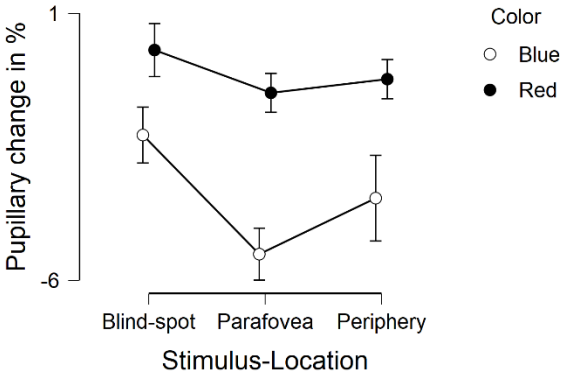

Figure 4: Mean and SEM of pupillary change in % at times < 1.7 s for blind-spot, parafovea and periphery stimulus location separated into blue and red light conditions.

3.2 Melanopsin at Times > 1.8 s

The repeated ANOVA revealed a significant main effect for color ($p < 0.01$), but not for stimulus location ($p = 0.48$) and their interaction ($p = 0.39$), see Table 2.

Table 2: ANOVA of PIPR at times > 1.8 s in detail.

	df	F	p	η^2_p
Stimulus location	2.28	0.75	0.48	0.02
Color	1.14	11.93	< 0.01	0.12
Stimulus location ∗ Color	2.28	0.96	0.39	0.01

Regarding color, post-hoc tests corrected with Tukey showed that pupil response to blue light is significantly larger than for the red light condition ($p < 0.01$), see Fig. 5.

In the red light condition for the parafovea condition and periphery condition, an overshoot after pupil constriction shortly before 2 s can be observed, which is not in the blind-spot condition, see Fig. 3. Therefore, PIPR at times 1 s > 1.8 s was analyzed only in blue light conditions in the following analysis. In order to test the hypothesis for no difference between blind-spot and periphery conditions, Bayesian analysis was conducted. Positive evidence (i.e., $BF_{01} = 3.2$, error = 0.003%) was observed comparing blind-spot and periphery at times 1 s > 1.8 s. An overlapping PIPR at times after 1.8 s is visible in Fig. 6 between blind-spot and periphery.

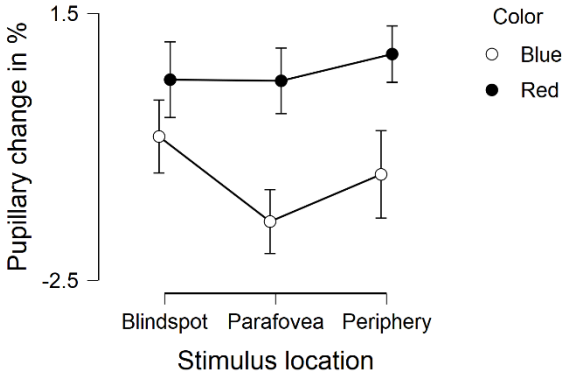

Figure 5: Mean and SEM of pupillary change in % for sustained pupillary response Melanopsin at times > 1.8 s for blind-spot, parafovea and periphery stimulus location separated into blue and red light conditions.

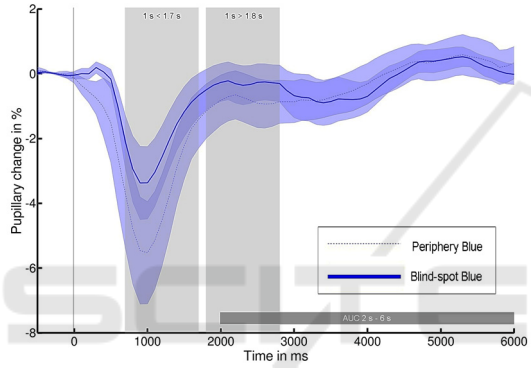

Figure 6: Pupillary change for blind-spot (solid line) and periphery (dotted line) condition for blue light condition. Stimulus onset is at 0 ms.

3.3 Melanopsin at Times 2 s – 6 s

For the AUC at times 2 s – 6 s, Bayesian analysis was conducted in order to test for no difference in PIPR after blue light stimulus between the blind-spot and periphery. Positive evidence (i.e., $BF_{01} = 3.81$, error = 0.003% was observed when comparing the blind-spot and periphery conditions.

Lastly, to test our hypothesis, due to no overshoot in blind-spot red light condition, a paired one-sided *t*-test comparison in the blind-spot condition showed a significantly larger pupillary change to blue light as compared to red light ($t(14) = -1.9$, $p = 0.043$, $d = -0.48$).

4 DISCUSSION

We characterized pupil responses after blue light stimulation in the blind-spot to investigate melanopsin contributions in the blind-spot compared to parafovea condition and periphery condition. Miyamoto and Murakami found that stimulation inside the blind-spot enhances, but does not trigger, the pupillary light reflex (Miyamoto & Murakami, 2015). A photo-sensitive mechanism inside the optic disk, which most likely involves melanopsin, has been suggested to provide a reference for calibrating the perceived brightness of visual objects (Saito et al., 2018). In this study, we further explored the presence of melanopsin in the blind-spot by investigating the sustained response of pupil constriction regarding melanopsin contribution to PIPR when stimulating the blind-spot solely.

At both times < 1.7 s and times > 1.8 s pupillary change in blue light conditions were larger than in the red light conditions independent of the stimulus location. This independency was indicated by the absence of a significant interaction between the two factors color and stimulus location. Therefore, we assume that melanopsin contributes to the sustained pupil response in the blind-spot, parafovea and periphery. This is consistent with previous work that described sustained pupil constriction by the spectral sensitivity of melanopsin (Gamlin et al., 2007). However, the difference between the blue and red light could also be explained by greater than a 0% pupillary change in the red light conditions, which could come from a dilating pupil, while the pupillary change was only slightly below 0% in blue light conditions.

The time window of 1 s before times < 1.7 s is reported to be influenced by the contribution of rhodopsin and melanopsin (Adhikari et al., 2016). Due to the absence of rods and cones in the optic disc, blind-spot stimulation is influenced less by rhodopsin than parafovea region is, which could explain the observed difference between the blind-spot condition and parafovea condition at times < 1.7 s. Furthermore, this difference between blind-spot and parafovea can be explained by the finding that red light does not trigger the pupil constriction in the blind-spot because of the absence of cones in the blind-spot, as shown before (Miyamoto & Murakami, 2015).

For the blind-spot condition, we would mainly expect the pupillary response to be influenced by melanopsin, whereas the periphery would be influenced by both rhodopsin and melanopsin.

Even when the light is focused exactly on the optic disc, there could be light hitting the retina on other locations than the target area due to light scattering. Small particles in the compartments of the eye, such as cornea and crystalline lens, and the

spectacles - if worn - can scatter light away from the target (van den Berg, Franssen, Kruijt, & Coppens, 2013), which would activate photoreceptors on the retina. Therefore, we implemented two control conditions in the periphery and parafovea. The scattered light profile is similar in blind-spot and periphery due to comparable location and similar stimulus characteristics. If scattering was the reason for blind-spot PIPR, we would have expected a larger PIPR in the periphery as compared to the blind-spot due to the extra rhodopsin contribution which is not present in the blind-spot; but both conditions have similar PIPRs. Earlier works have provided further arguments to rule out a substantial influence by scattered light when stimulating the blind-spot (Saito et al., 2018). Still, we cannot completely exclude that the remaining scattered light may stimulate rods to modulate the pupil response in our experiment.

There are a few reasons for choosing the parafoveal location. First, in the central fovea there are no RGCs between the entering light and the photoreceptor layer. To have comparable condition to the blind-spot and periphery, the stimulus was placed at the outer edge of the parafoveal region, where RGCs project away from the fovea. Secondly, potential filtering by the macular pigment is expected to be reduced when moving from the center towards the periphery as compared to the central fovea. Finally, no cells containing melanopsin have been reported in the central retina (Dacey et al., 2005; Liao et al., 2016; Nasir-Ahmad, Lee, Martin, & Grünert, 2019); therefore, to target melanopsin containing cells, we stimulated near the fovea in the parafovea region.

Previous studies have shown that pupil response can be induced by purely activating melanopsin, for example see (Woelders et al., 2018). Furthermore, pupil response is intact in cone-less and rod-less mice with a peak sensitivity at 479 nm (Lucas et al., 2001). Nevertheless, there was no difference between periphery and blind-spot, which could be explained by the presence of melanopsin in the blind-spot, because the pupil response in the periphery should be driven by both rhodopsin and melanopsin. To date, we are not aware of any systematic comparison between melanopsin concentration in the blind-spot and other regions, but it has been shown that the concentration of melanopsin cells is higher near the human fovea when compared to the periphery (Nasir-Ahmad et al., 2019). Such a difference between parafovea and periphery was not evidenced in our data, probably because our peripheral condition was not far enough in the periphery. We would expect a decrease in the sustained pupil response with a more eccentric peripheral condition that can be subject to future studies.

Looking only at blue light conditions, the Bayesian analysis provided support for the null hypothesis that there is no difference between blind-spot and periphery PIPR; indicating an equal contribution of melanopsin in both conditions. One explanation for the similarity in the sustained signal among all stimulus location for the blue light condition could be that blind-spot contains as much melanopsin as the parafovea and periphery.

The limitation of this comparison among the blue light conditions is that BF_{01} was uncorrected and no strong or very strong evidence was found, however it showed positive evidence for the absence of a difference in PIPR between the blind-spot and periphery. One possible explanation would be that only two trials per stimulus condition were recorded and no trials were excluded. Furthermore, we looked closer at the blue light conditions only at times 1 s > 1.8 s for the following reason: the red light condition in blind-spot seems to increase pupil size continuously, because no input triggered the pupil size change and the pupil was not dark adapted and therefore not stable. Moreover, an overshoot after pupil constriction was noticeable in the red light conditions, except in the blind-spot condition, likely because there was no pupil constriction. This overshoot could affect the calculation of the melanopsin response at times 1 s > 1.8 s, if the red light condition was the reference.

However, this overshoot in the red light condition was not visible for the blind-spot. Therefore, it allows a comparison between blue and red light in the blind-spot. This comparison confirmed our hypothesis that blue light constricts the pupil more than red light when shone in the blind-spot. To our knowledge, this sustained pupil constriction in the blind-spot is a novel finding and suggests the presence of melanopsin in the blind-spot.

Previous work found that pupil response is enhanced by blue light as compared to red light inside the blind-spot, when outside blind-spot was also illuminated (Miyamoto & Murakami, 2015). Miyamoto and Murakami speculated that this is modulated by melanopsin in the blind-spot. Our results provide further support for the presence of melanopsin in the blind-spot. Similarly, the AUC between 2 s – 6 s showed that blue light stimulation in the blind-spot keeps the pupil constricted for a longer time as compared to red light; which suggests a contribution of blind-spot melanopsin to the PIPR.

5 CONCLUSIONS

In conclusion blue light stimulation inside blind-spot and outside blind-spot in the peripheral retina revealed a comparable PIPR, although there are no rods and cones in the optic disc. In the absence of classical photoreceptors, melanopsin seems to be responsible for pupil constriction when light is shone in the blind-spot. This supports the presence of melanopsin on the axons of ipRGCs at the head of optic nerve, which can constitute potential applications of stimulating melanopsin with visible light, although invisible to the observer.

ACKNOWLEDGEMENTS

This work was supported by the Federal Ministry of Education and Research, Industrie-in-Klinik-Plattform Program BMBF, Germany (FKZ: 13GW0256). MS was supported by the DFG grant [NU 265/3-1] to HCN. MS and HCN are members of the LEAD Research Network [GSC1028], which is funded within the framework of the Excellence Initiative of the German federal and state governments. We would like to thank Zoë Kirste for language proofreading.

REFERENCES

Adhikari, P., Feigl, B., & Zele, A. J. (2016). Rhodopsin and melanopsin contributions to the early redilation phase of the post-illumination pupil response (PIPR). *PLoS One*, *11*(8), e0161175.

Adhikari, P., Zele, A. J., & Feigl, B. (2015). The post-illumination pupil response (PIPR). *Investigative Ophthalmology & Visual Science*, *56*(6), 3838–3849.

Alpern, M., & Campbell, F. W. (1962). The spectral sensitivity of the consensual light reflex. *The Journal of Physiology*, *164*(3), 478–507.

Bach, M. (2006). The Freiburg Visual Acuity Test-variability unchanged by post-hoc re-analysis. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *245*(7), 965–971.

Berson, D. M., Dunn, F. A., & Takao, M. (2002). Phototransduction by retinal ganglion cells that set the circadian clock. *Science*, *295*(5557), 1070–1073.

Dacey, D. M., Liao, H.-W., Peterson, B. B., Robinson, F. R., Smith, V. C., Pokorny, J., … Gamlin, P. D. (2005). Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. *Nature*, *433*(7027), 749.

Fu, Y., Zhong, H., Wang, M. H., Luo, D., Liao, H., Maeda, H., … Yau, K. (2005). Intrinsically Photosensitive Retinal Ganglion Cells Detect Light With a Vitamin A–Based Photopigment That is Most Likely Melanopsin. *Investigative Ophthalmology & Visual Science*, *46*(13), 2238.

Gamlin, P. D. R., McDougal, D. H., Pokorny, J., Smith, V. C., Yau, K.-W., & Dacey, D. M. (2007). Human and macaque pupil responses driven by melanopsin-containing retinal ganglion cells. *Vision Research*, *47*(7), 946–954.

Hattar, S., Liao, H.-W., Takao, M., Berson, D. M., & Yau, K.-W. (2002). Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science*, *295*(5557), 1065–1070.

Hattar, S., Lucas, R. J., Mrosovsky, N., Thompson, S., Douglas, R. H., Hankins, M. W., … Foster, R. G. (2003). Melanopsin and rod–cone photoreceptive systems account for all major accessory visual functions in mice. *Nature*, *424*(6944), 75.

Hess, C. v. (1908). Untersuchungen zur Physiologie und Pathologie des Pupillenspieles. *Arch. f. Augenheilk*, *60*, 327–389.

John W. Eaton, David Bateman, Søren Hauberg, R. W. (2018). GNU Octave version 4.4.1 manual: a high-level interactive language for numerical computations.

Kass, R. E., & Raftery, A. E. (1995). Bayes factors. *Journal of the American Statistical Association*, *90*(430), 773–795.

Kelbsch, C., Strasser, T., Chen, Y., Feigl, B., Gamlin, P. D., Kardon, R., … Szabadi, E. (2019). Standards in pupillography. *Frontiers in Neurology*, *10*.

Liao, H., Ren, X., Peterson, B. B., Marshak, D. W., Yau, K., Gamlin, P. D., & Dacey, D. M. (2016). Melanopsin-expressing ganglion cells on macaque and human retinas form two morphologically distinct populations. *Journal of Comparative Neurology*, *524*(14), 2845–2872.

Lucas, R. J., Douglas, R. H., & Foster, R. G. (2001). Characterization of an ocular photopigment capable of driving pupillary constriction in mice. *Nature Neuroscience*, *4*(6), 621.

Lucas, R. J., Hattar, S., Takao, M., Berson, D. M., Foster, R. G., & Yau, K.-W. (2003). Diminished pupillary light reflex at high irradiances in melanopsin-knockout mice. *Science*, *299*(5604), 245–247.

Miyamoto, K., & Murakami, I. (2015). Pupillary light reflex to light inside the natural blind spot. *Scientific Reports*, *5*, 11862.

Münch, M., Léon, L., Crippa, S. V, & Kawasaki, A. (2012). Circadian and wake-dependent effects on the pupil light reflex in response to narrow-bandwidth light pulses. *Investigative Ophthalmology & Visual Science*, *53*(8), 4546–4555.

Mure, L. S., Cornut, P.-L., Rieux, C., Drouyer, E., Denis, P., Gronfier, C., & Cooper, H. M. (2009). Melanopsin bistability: a fly's eye technology in the human retina. *PLoS One*, *4*(6), e5991.

Nasir-Ahmad, S., Lee, S. C. S., Martin, P. R., & Grünert, U. (2019). Melanopsin-expressing ganglion cells in human retina: Morphology, distribution, and synaptic connections. *Journal of Comparative Neurology*, *527*(1), 312–327.

Park, J. C., Moura, A. L., Raza, A. S., Rhee, D. W., Kardon, R. H., & Hood, D. C. (2011). Toward a clinical protocol for assessing rod, cone, and melanopsin contributions to the human pupil response. *Investigative Ophthalmology & Visual Science*, *52*(9), 6624–6635.

Saito, M., Miyamoto, K., Uchiyama, Y., & Murakami, I. (2018). Invisible light inside the natural blind spot alters brightness at a remote location. *Scientific Reports*, *8*(1), 7540.

Van den Berg, T. J. T. P., Franssen, L., Kruijt, B., & Coppens, J. E. (2013). History of ocular straylight measurement: a review. *Zeitschrift Für Medizinische Physik*, *23*(1), 6–20.

Webster, J. G. (1969). Critical duration for the pupillary light reflex. *JOSA*, *59*(11), 1473–1478.

Woelders, T., Leenheers, T., Gordijn, M. C. M., Hut, R. A., Beersma, D. G. M., & Wams, E. J. (2018). Melanopsin- and L-cone–induced pupil constriction is inhibited by S-and M-cones in humans. *Proceedings of the National Academy of Sciences*, *115*(4), 792–797.