Photoreceptor inputs to pupil control

Manuel Spitschan

Department of Experimental Psychology, University of Oxford, Oxford, UK
Centre for Chronobiology, Psychiatric Hospital of the University of Basel (UPK), Basel, Switzerland
Transfaculty Research Platform Molecular and Cognitive Neurosciences, University of Basel, Basel, Switzerland

The size of the pupil depends on light level. Watson and Yellott (2012) developed a unified formula to predict pupil size from luminance, field diameter, age, and number of eyes. Luminance reflects input from the L and M cones in the retina but ignores the contribution of intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing the photopigment melanopsin, which are known to control the size of the pupil. We discuss the role of melanopsin in controlling pupil size by reanalyzing an extant data set (Bouma, 1962). We confirm that melanopsin-weighted quantities, in conjunction with Watson and Yellott's formula, adequately model intensity-dependent pupil size. We discuss the contributions of other photoreceptors into pupil control.

In a paper adequately described as a *tour de force*, Watson and Yellott (2012) developed a unified formula to predict pupil size from luminance, field diameter, age, and number of eyes.[1] This letter concerns the parametrization of the retinal intensity, which in Watson and Yellott's model is given in terms of luminance, i.e., the radiance of the stimulus weighted by the photopic luminosity curve V(λ). V(λ) corresponds to a mixture of the L and M cones in the retina, thereby largely ignoring the potential role of S cones, rods, and the intrinsically photosensitive retinal ganglion cells (ipRGCs) expressing the photopigment melanopsin (Dacey et al., 2005; Gamlin et al., 2007; Provencio et al., 2000).

The observation that V(λ)-weighted quantities do not predict pupil size is not new (Berman, Fein, Jewett, Saika, & Ashford, 1992; Krastel, Alexandridis, & Gertz, 1985). Already in 1962, Bouma (1962) noted that the spectral sensitivity of pupil control is neither V(λ) nor the rod-based V'(λ), conjecturing that the outcome of his experiments "may turn out to be related to other adaptive processes in the human eye". Bouma himself modeled the spectral sensitivity as a combination of S cones and rods. We know now that steady-state pupil size is largely controlled by melanopsin.

To test if Bouma's (1962) data are consistent with melanopsin-based pupil control, we reanalyzed the intensity-response curves from Bouma as follows. We first extracted the data from Bouma's figure 1, as shown in our Figure 1A and B using WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/). For monochromatic lights, which we assumed Bouma used, it is simple to convert the reported V(λ)-weighted luminous flux into a melanopsin-weighted radiant flux (Commission Internationale de l'Eclairage [CIE], 2018). As radiant flux describes the total amount of energy emitted by a source, it is not an appropriate measure to describe corneal or retinal illumination, so the absolute quantities are not informative unless a geometry is specified. Allowing for fixed but arbitrary horizontal shift, the data for all wavelengths now coincide, except for long-wavelength lights (Figure 1C). In addition, Watson and Yellott's (2012) formula (red line) accounts well for the shape of the pupil response as a function of normalized melanopic radiant flux.

One notable and systematic deviation occurs for the 670-nm data points, which a melanopsin-exclusive model appears not to predict well. This suggests that melanopsin is not the only photoreceptor controlling steady-state pupil size. This is not surprising, as melanopsin-containing retinal ganglion cells receive cone and rod inputs (Dacey et al., 2005).

Indeed, there is now a good body of evidence that all photoreceptors can control the diameter of the pupil. The best evidence comes from studies examining pupil size using the method of silent substitution, in which pairs of lights are alternated such that only one photoreceptor class is stimulated (Estévez & Spekreijse, 1982; Spitschan & Woelders, 2018). Studies examining pupil control using this method are given in Table 1.

A key realization is that while all photoreceptors may contribute to controlling the pupil size, the *when*

Citation: Spitschan, M. (2019). Photoreceptor inputs to pupil control. *Journal of Vision*, *19*(9):5, 1–5, https://doi.org/10.1167/19.9.5.

https://doi.org/10.1167/19.9.5 Received May 1, 2019; published August 15, 2019 ISSN 1534-7362

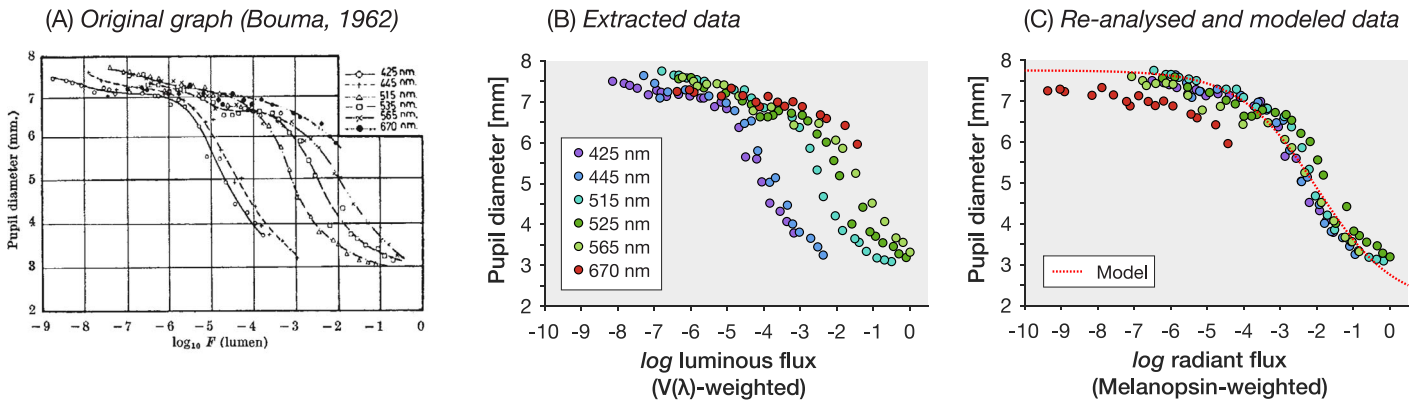

Figure 1. (A) Original graph from Bouma (1962) relating luminous flux to pupil diameter in millimeters. From "Size of the static pupil as a function of wave-length and luminosity of the light incident on the human eye," by H. Bouma, 1962, *Nature*, *193*(4816), 690–691. Copyright 1962 by Springer Nature. Reprinted with permission. (B) Replotted extracted pupil size data. (C) Data replotted in terms of normalized melanopic radiant flux, along with the unified formula by Watson and Yellott (2012), allowing for a horizontal shift aligning the data with the curve.

Photoreceptor class	Reference
Melanopsin	Tsujimura, Ukai, Ohama, Nuruki, and Yunokuchi (2010)
	Viénot, Bailacq, and Rohellec (2010)
	Tsujimura and Tokuda (2011)
	Spitschan et al. (2014)
	Cao, Nicandro, and Barrionuevo (2015)
	Barrionuevo and Cao (2016)
	Spitschan et al. (2017)
	Zele, Feigl, Adhikari, Maynard, and Cao (2018)
L cone	Spitschan et al. (2014) (L+M)
	Spitschan et al. (2017) (L+M+S)
	Barrionuevo and Cao (2016)
	Murray, Kremers, McKeefry, and Parry (2018)
	Woelders et al. (2018)
M cone	Spitschan et al. (2014) (L+M)
	Spitschan et al. (2017) (L+M+S)
	Barrionuevo and Cao (2016)
	Murray et al. (2018)
	Woelders et al. (2018)
S cone	Viénot, Bailacq, and Rohellec (2010)
	Spitschan et al. (2014)
	Spitschan et al. (2017)
	Barrionuevo and Cao (2016)
	Cao et al. (2015)
	Murray et al. (2018)
	Woelders et al. (2018)
Rods	Barrionuevo, McAnany, Zele, and Cao (2018)
	Barrionuevo et al. (2014)

Table 1. Evidence of photoreceptor contributions to pupil control.

and *how* is important. For example, due to rod saturation (Aguilar & Stiles, 1954), rods are not expected to contribute to pupil control at photopic light levels. The temporal regimes in which the photoreceptors contribute are also different. Notably, L+M stimulation is band-pass, while S cones and melanopsin are tuned to low frequencies in driving the pupil (Spitschan, Jain, Brainard, & Aguirre, 2014). McDougal and Gamlin (2010) found that cones and rods account for pupil constriction between 1 and 10 s from the onset of the light exposure; at 100 s, pupil size is largely controlled by melanopsin with some contribution from the rods.

To what extent does Watson and Yellott's (2012) use of luminance as an input parameter call into question the generalizability of their model? From first principles, differences between V(λ)-weighted and melanopic quantities are largest with monochromatic lights. But we typically do not live under monochromatic illumination. We explored this question by examining the range of melanopic irradiances at a fixed illuminance. In other words, how wrong would we be if we continued using V(λ)-weighted quantities to predict pupil size?

Using a database of 401 polychromatic ("white") illuminant spectra (Houser, Wei, David, Krames, & Shen, 2013), we calculated the range of melanopic irradiance while keeping the photopic illuminance fixed at 100 lux (Figure 2A). Across all 401 spectra, a 100 lux light source has a melanopic irradiance of 75.5 ± 23.4 mW/m^2. Crucially, the melanopic irradiance of an illuminant at 100 lux depends also on the correlated color temperature (CCT) of the source (Figure 2B), with higher, more bluish CCT illuminants generally having a higher melanopic irradiance. Irrespective of CCT, the range of melanopic irradiances is between 20.4 and 164 melanopic mW/m^2, i.e., in the worst case a

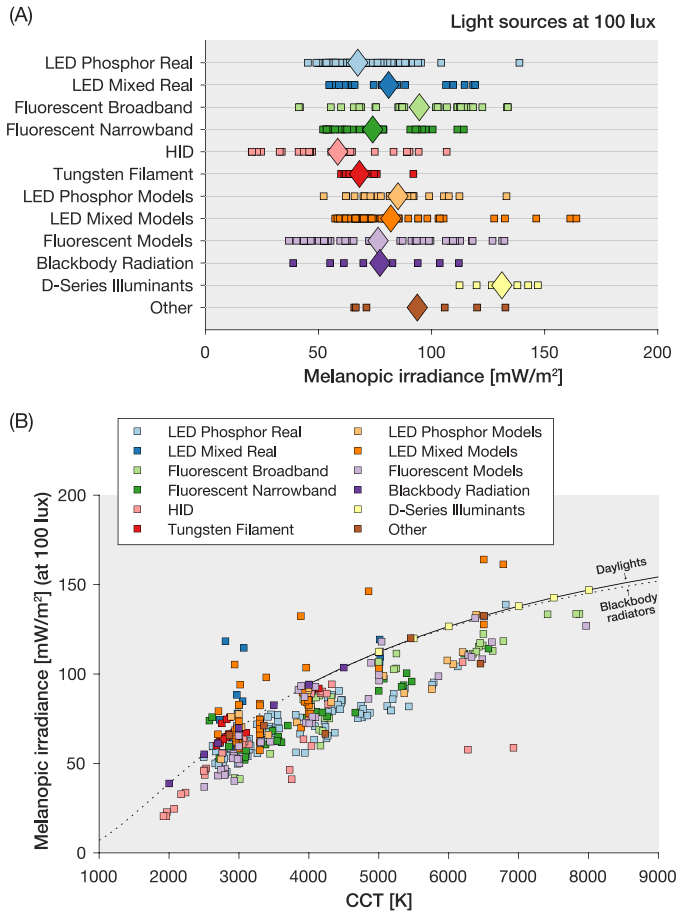

Figure 2. (A) Variability of the melanopic irradiance of 401 polychromatic "white" light sources (Houser et al., 2013) at 100 lux. Individual sources are represented as individual dots. Large diamonds are the per-category mean. Houser et al. (2013) considered both real and theoretical (i.e., model-based) light sources. Details on the nomenclature and provenance of the light source can be found in (Houser et al., 2013). (B) Melanopic irradiance as a function of the CCT. Continuous line indicates daylights; dashed line indicates blackbody radiators.

factor of ~8. In other words, using a V(λ)-based pupil formula could lead to a misrepresentation of the retinal intensity by up to one order of magnitude ($\log_{10}(8) = 0.9$), which manifests in the horizontal shift of the intensity response curve in Figure 1A and B.

The degree of misestimation of pupil size from a V(λ)-based model depends on the retinal intensity (as the curve is nonlinear). It is also conceivable that the diversity in pupil formulæ found by Watson and Yellott (2012) could simply reflect the fact that previous investigators used different spectral power distributions, which had the same (il)luminance but differed in their melanopic (ir)radiance.

Whether or not the worst-case misprediction by using a V(λ)-weighted quantity has tangible consequences depends on the application. Predicting pupil size in a psychophysical experiment at mesopic light levels requires less stringent estimation of retinal intensity than safety-critical calculations.

A recent study reported an attempt to derive a formula for predicting pupil size from melanopsin activation but only focused on a rather narrow luminance range (50–300 cd/m^2; Rao, Chan, & Zhu, 2017). While this is a good start, it might be a useful empirical exercise to collect natural pupil sizes under a large range of illumination conditions (indoors, outdoors) under natural behavior with conjoint spectral measurements. Our analysis of pupil size as a function of melanopic retinal intensity provides a starting point for predicting pupil size from the spectral properties of a scene.

Keywords: melanopsin, pupil, cones, photoreceptors

Acknowledgments

MS is supported by a Sir Henry Wellcome Trust Fellowship (Wellcome Trust 204686/Z/16/Z) and a Junior Research Fellowship from Linacre College, University of Oxford. All data and code, including a MATLAB implementation of Watson and Yellott's unified formula, are available at https://github.com/spitschan/Spitschan2019_JOV. We thank Rafael Lazar for assistance in data extraction.

Commercial relationships: none.
Corresponding author: Manuel Spitschan.
Email: manuel.spitschan@psy.ox.ac.uk.
Address: Department of Experimental Psychology, University of Oxford, Oxford, UK.

Footnote

[1] The Watson and Yellott (2012) article contains two typos. In their equation 13, the last term, 0.07(log L)^2, should be subtracted, not added. In their equation 14, the term s_3 is missing a minus sign. Their supplementary Mathematica notebook and our reimplementation (at https://github.com/spitschan/Spitschan2019_JOV) does not contain these errors.

References

Aguilar, M., & Stiles, W. S. (1954). Saturation of the rod mechanism of the retina at high levels of stimulation. *Optica Acta*, *1*(1), 59–65, https://doi.org/10.1080/713818657.

Barrionuevo, P. A., & Cao, D. (2016). Luminance and

chromatic signals interact differently with melanopsin activation to control the pupil light response. *Journal of Vision*, *16*(11):29, 1–17, https://doi.org/10.1167/16.11.29. [PubMed] [Article]

Barrionuevo, P. A., McAnany, J. J., Zele, A. J., & Cao, D. (2018). Non-linearities in the rod and cone photoreceptor inputs to the afferent pupil light response. *Frontiers in Neurology*, *9*, 1140, https://doi.org/10.3389/fneur.2018.01140.

Barrionuevo, P. A., Nicandro, N., McAnany, J. J., Zele, A. J., Gamlin, P., & Cao, D. (2014). Assessing rod, cone, and melanopsin contributions to human pupil flicker responses. *Investigative Ophthalmology & Visual Science*, *55*(2), 719–727, https://doi.org/10.1167/iovs.13-13252.

Berman, S. M., Fein, G., Jewett, D. L., Saika, G., & Ashford, F. (1992). Spectral determinants of steady-state pupil size with full field of view. *Journal of the Illuminating Engineering Society*, *21*(2), 3–13, https://doi.org/10.1080/00994480.1992.10747995.

Bouma, H. (1962, February 17). Size of the static pupil as a function of wave-length and luminosity of the light incident on the human eye. *Nature*, *193*(4816), 690–691, https://doi.org/10.1038/193690a0.

Cao, D., Nicandro, N., & Barrionuevo, P. A. (2015). A five-primary photostimulator suitable for studying intrinsically photosensitive retinal ganglion cell functions in humans. *Journal of Vision*, *15*(1):27, 1–13, https://doi.org/10.1167/15.1.27. [PubMed] [Article]

Commission Internationale de l'Eclairage [CIE]. (2018). CIE S 026/E:2018 - CIE system for metrology of optical radiation for ipRGC-influenced responses to light. Vienna, Austria: CIE Central Bureau. https://doi.org/10.25039/S026.2018.

Dacey, D. M., Liao, H. W., Peterson, B. B., Robinson, F. R., Smith, V. C., Pokorny, J., ... Gamlin, P. D. (2005, February 17). Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. *Nature*, *433*(7027), 749–754, https://doi.org/10.1038/nature03387.

Estévez, O., & Spekreijse, H. (1982). The "silent substitution" method in visual research. *Vision Research*, *22*(6), 681–691, https://doi.org/10.1016/0042-6989(82)90104-3.

Gamlin, P. D., 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, https://doi.org/10.1016/j.visres.2006.12.015.

Houser, K. W., Wei, M., David, A., Krames, M. R., & Shen, X. S. (2013). Review of measures for light-source color rendition and considerations for a two-measure system for characterizing color rendition. *Optics Express*, *21*(8), 10393–10411, https://doi.org/10.1364/OE.21.010393.

Krastel, H., Alexandridis, E., & Gertz, J. (1985). Pupil increment thresholds are influenced by color opponent mechanisms. *Ophthalmologica*, *191*(1), 35–38, https://doi.org/10.1159/000309536.

McDougal, D. H., & Gamlin, P. D. (2010). The influence of intrinsically-photosensitive retinal ganglion cells on the spectral sensitivity and response dynamics of the human pupillary light reflex. *Vision Research*, *50*(1), 72–87, https://doi.org/10.1016/j.visres.2009.10.012.

Murray, I. J., Kremers, J., McKeefry, D., & Parry, N. R. A. (2018). Paradoxical pupil responses to isolated M-cone increments. *Journal of the Optical Society of America, A: Optics, image Science, and Vision*, *35*(4), B66–B71, https://doi.org/10.1364/JOSAA.35.000B66.

Provencio, I., Rodriguez, I. R., Jiang, G., Hayes, W. P., Moreira, E. F., & Rollag, M. D. (2000). A novel human opsin in the inner retina. *Journal of Neuroscience*, *20*(2), 600–605, https://doi.org/10.1523/JNEUROSCI.20-02-00600.2000.

Rao, F., Chan, A. H. S., & Zhu, X. F. (2017). Effects of photopic and cirtopic illumination on steady state pupil sizes. *Vision Research*, *137*, 24–28, https://doi.org/10.1016/j.visres.2017.02.010.

Spitschan, M., Bock, A. S., Ryan, J., Frazzetta, G., Brainard, D. H., & Aguirre, G. K. (2017). The human visual cortex response to melanopsin-directed stimulation is accompanied by a distinct perceptual experience. *Proceedings of the National Academy of Sciences, USA*, *114*(46), 12291–12296, https://doi.org/10.1073/pnas.1711522114.

Spitschan, M., Jain, S., Brainard, D. H., & Aguirre, G. K. (2014). Opponent melanopsin and S-cone signals in the human pupillary light response. *Proceedings of the National Academy of Sciences, USA*, *111*(43), 15568–15572, https://doi.org/10.1073/pnas.1400942111.

Spitschan, M., & Woelders, T. (2018). The method of silent substitution for examining melanopsin contributions to pupil control. *Frontiers in Neurology*, *9*, 941, https://doi.org/10.3389/fneur.2018.00941.

Tsujimura, S., & Tokuda, Y. (2011). Delayed response of human melanopsin retinal ganglion cells on the pupillary light reflex. *Ophthalmic & Physiological*

Optics, *31*(5), 469–479, https://doi.org/10.1111/j.1475-1313.2011.00846.x.

Tsujimura, S., Ukai, K., Ohama, D., Nuruki, A., & Yunokuchi, K. (2010). Contribution of human melanopsin retinal ganglion cells to steady-state pupil responses. *Proceedings of the Royal Society, B: Biological Sciences*, *277*(1693), 2485–2492, https://doi.org/10.1098/rspb.2010.0330.

Viénot, F., Bailacq, S., & Rohellec, J. L. (2010). The effect of controlled photopigment excitations on pupil aperture. *Ophthalmic and Physiological Optics*, *30*(5), 484–491, https://doi.org/10.1111/j.1475-1313.2010.00754.x.

Watson, A. B., & Yellott, J. I. (2012). A unified formula for light-adapted pupil size. *Journal of Vision*, *12*(10):12, 1–16, https://doi.org/10.1167/12.10.12. [PubMed] [Article]

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, USA*, *115*(4), 792–797, https://doi.org/10.1073/pnas.1716281115.

Zele, A. J., Feigl, B., Adhikari, P., Maynard, M. L., & Cao, D. (2018). Melanopsin photoreception contributes to human visual detection, temporal and colour processing. *Scientific Reports*, *8*(1), 3842, https://doi.org/10.1038/s41598-018-22197-w.