

# Effect of Pharmacological Pupil Dilation on Dark-Adapted Perimetric Sensitivity in Healthy Subjects Using an Octopus 900 Perimeter

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**Purpose:** To determine whether dilation status has a clinically meaningful effect on sensitivity in normal subjects undergoing two-color dark-adapted perimetry, which can be useful to assess rod function.

**Methods:** A perimeter measured naturally and pharmacologically dilated scotopic sensitivities using a test grid consisting of 16 points across the horizontal meridian ranging from 60° temporal to 45° nasal using cyan (500 nm wavelength) or red (650 nm wavelength) stimuli. The primary outcome was average overall sensitivity based on dilation status, which was compared using a linear mixed effect model for each color stimuli. A difference of 2 dB or more was considered clinically significant.

**Results:** Twenty-nine eyes from 15 subjects (nine female) ages 23 to 63 with no known retinal pathology were included. Pharmacologically dilated eyes were 0.54 dB (95% confidence interval [CI], 0.05 dB to 1.03 dB;  $P = 0.032$ ) more sensitive to a red stimulus than naturally dilated eyes, but this was not statistically significant after correction for multiple comparisons. Pharmacologically dilated eyes were 0.03 dB (95% CI, -0.20 dB to 0.14 dB;  $P = 0.734$ ) less sensitive to a cyan stimulus compared to naturally dilated eyes.

**Conclusions:** These findings show no clinically significant differences in sensitivity of scotopic perimetry in eyes without retinal pathology based on dilation status for both cyan and red stimuli.

**Translational Relevance:** In this study, pharmacological dilation did not have a clinically meaningful effect on sensitivity, suggesting that this is not necessary when using two-color dark-adapted perimetry to assess for rod function.

## Introduction

Psychophysical assessments have long been a vital measure of visual function in ophthalmology, which include best-corrected visual acuity, color discrimination tests, and visual field tests or perimetry. Historically, full field kinetic perimetry (e.g., Goldmann visual field) was generally used to assess visual field constriction and scotomas in neuro-ophthalmology and inherited retinal degenerations, whereas static

perimetry of the central field from 10° to 30° (e.g., Humphrey, Maia, or Nidek microperimetry) was typically used to evaluate and monitor glaucomatous damage and retinopathies that involve the macula. The advent of full field static perimetry (e.g., Haag-Streit Octopus 900; Haag-Streit AG, Koenig, Switzerland; Medmont; Medmont International Pty Ltd., Nunawading, Australia) allows localization and quantification of the rate of retinal degeneration throughout the visual field permitting better development of endpoints in clinical trials for inherited

retinal degenerations. However, most perimetry protocols are performed under light-adapted or photopic testing conditions, which is mainly an assessment of light-adapted cone photoreceptor function.<sup>1-3</sup> Because inherited retinal degenerations such as retinitis pigmentosa primarily affect the rod photoreceptors in early-to moderate-stage disease, there is a growing need to develop more sophisticated protocols that have the ability to isolate dark-adapted (scotopic) rod function, such as two-color dark-adapted perimetry (2cDAP). Spectral sensitivity studies have shown that rods are approximately 2 log-fold more sensitive to a 500 nm stimulus versus a 650 nm stimulus, whereas cones are approximately equally sensitive to 500 nm and 650 nm stimuli.<sup>4</sup> Therefore any response measured by 2cDAP that shows a significantly higher sensitivity to a 500 nm stimulus versus a 650 nm stimulus can be determined to be a rod-mediated response. Study protocols for dark-adapted full field perimetry and microperimetry often involve pharmacological pupil dilation before testing,<sup>5-11</sup> although the effect of pharmacological dilation on 2cDAP has not been fully elucidated.

Dilation status has been shown to significantly affect sensitivity in photopic perimetry testing in normal and glaucomatous eyes; sensitivity of normal eyes decreased by 0.83 dB and 0.87 dB and sensitivity of glaucomatous eyes decreased by 3.01 dB after pharmacological dilation.<sup>12-14</sup> In contrast, the effect of pharmacological dilation on macular sensitivity using two-color mesopic microperimetry in normal eyes and eyes with choroideremia was shown not to be statistically significant.<sup>15</sup> The aforementioned study used microperimetry, which is useful to look at central sensitivity in patients with advanced disease but not peripheral points such as measured by 2cDAP and is fundus guided using a Maxwellian view versus the standard view perimetry like 2cDAP.

The effect of pharmacological dilation on dark-adapted perimetric sensitivity has not been reported. Under dark-adapted conditions the pupil is naturally dilated, which predicts that pharmacological dilation should not affect perimetric sensitivity. However, pharmacological dilation may produce a larger pupil size than that achieved by natural dilation under dark-adapted conditions. A recent study evaluating the pupillary size in healthy adults showed an average pupillary diameter of 6.06 mm while naturally dilated under dark-adapted conditions without any pharmacological intervention and an average pupillary diameter of 7.94 mm when dilated with tropicamide and phenylephrine.<sup>16</sup> Small differences in pupil diameter under these conditions may affect sensitivity given the exponential difference in pupil area. A change from 6.06 mm to 7.94 mm results in a 31% increase in

pupil diameter and a 72% increase in pupil area. This may result in greater sensitivity in pharmacologically dilated subjects compared to naturally dilated subjects under dark-adapted conditions. In addition, pharmacological dilation with tropicamide affects accommodation, which may also influence sensitivity. Pupillary dilation also affects the angle of light that can enter the pupil and the angle it makes relative to the photoreceptors, which can lead to differences in sensitivity based on the Stiles-Crawford effect. This may result in variable sensitivity based on dilation status. However, the Stiles-Crawford effect is cone mediated and may not be as clinically relevant under scotopic conditions where the highest sensitivity is likely mediated by rods at most points outside of the fovea. Finally, the effect of dilation status may be moderated by other factors such as age. Previous studies have suggested that 2cDAP sensitivity decreases with increasing age; however, there are no studies evaluating whether this modifies the effect of dilation status.<sup>6,17</sup> This may result in dilation status being significant in some populations but not in others. At present, the effect of pharmacological dilation on dark-adapted perimetric sensitivity is uncertain. Here we present the results of a study to understand the relationship between pupil dilation and 2cDAP sensitivity in healthy adults to determine any clinically significant difference between conditions.

## Methods

This study was approved by the Institutional Review Board of Oregon Health & Science University and met the tenets of the Declaration of Helsinki. All subjects were appropriately consented.

## Testing Strategy

Perimetry was performed with a modified Octopus 900 Perimeter (Haag-Streit) using 500 nm (cyan) and 650 nm (red) filters. Light baffling was used on the perimeter and in the testing room to prevent ambient light escape. Absence of scattered ambient light was confirmed with a Konica Minolta 100LS (Konica Minolta, Tokyo, Japan) that read 0.000 cd/m<sup>2</sup> within the bowl of the perimeter. We used a horizontal grid with size III Goldmann targets tested at 16 points across the horizontal meridian ranging from 60° temporal to 45° nasal to nasal. The maximum luminance (i.e., the 0 dB luminance) values were 63.5 cd/m<sup>2</sup> and 174 cd/m<sup>2</sup> for the red and cyan stimuli, respectively. Healthy adult volunteers with no known retinal pathology of the tested eyes performed

a practice light-adapted perimetry under both red and cyan conditions. They then underwent a 45-minute dark adaptation followed by natural dilation (ND) testing. Pharmacological dilation (PD) was then performed using one drop of phenylephrine hydrochloride 2.5% and one drop of tropicamide 1%. Subjects were pharmacologically dilated in dark-adapted conditions for 20 minutes, and PD testing followed. Subjects who returned for the second ND testing session completed the same 45-minute dark adaptation followed by ND testing at a later date. All testing was performed with the red stimulus followed by the cyan.

The sensitivity of each of the 16 points was measured for each participant under each condition and was recorded in decibels of attenuation (dB). Points 30° or further from the fovea were classified as peripheral, and points within 30° of the fovea were classified as central.

## Clinical Significance

This study was primarily concerned with detecting a clinically, not statistically, significant difference based on dilation status. Bennet et al.<sup>6</sup> showed that the range of the upper limit to the lower limit of agreement in intrasession variability was  $-2$  dB to  $+2$  dB. Therefore clinical significance was a priori defined as a difference in mean sensitivity  $\geq 2$  dB.

## Subject Characteristics

Twenty-nine eyes of 15 healthy adults, of which nine were female, were included in this study. Age at the time of testing ranged from 23 to 63 years, with a mean of 42.1 years. Fourteen (eight female) of these subjects (27 eyes), returned for repeat ND testing, with ages ranging from 23 to 63 years with a mean of 43.1 years. The mean time between the first and second test dates was 26.6 days (range 7–67 days).

## Statistical Analysis and Model Diagnostics

The primary outcome was the difference between the overall sensitivity between ND and PD conditions for each color stimulus. Secondary outcomes were the differences in the peripheral and central sensitivity between ND and PD conditions, the overall sensitivity between the first ND and second ND tests, the effect of age on the overall sensitivity, and the interaction between age and dilation status on overall sensitivity for both color stimuli.

Primary and secondary endpoints were evaluated using linear mixed effect models nesting eyes within

each individual. We chose a linear mixed effect model as we were interested in effect size and wanted to account for the correlation between eyes. The residuals were largely normal except for one outlier. However, given that all of the values for the outlier were lowered by a relatively equal amount, the differences based on condition (i.e., dilation status and visit number) were similar for the outlier and the nonoutliers. Consequently, there was minimal change in the models when including and excluding the outlier. All individuals were kept in the final models.

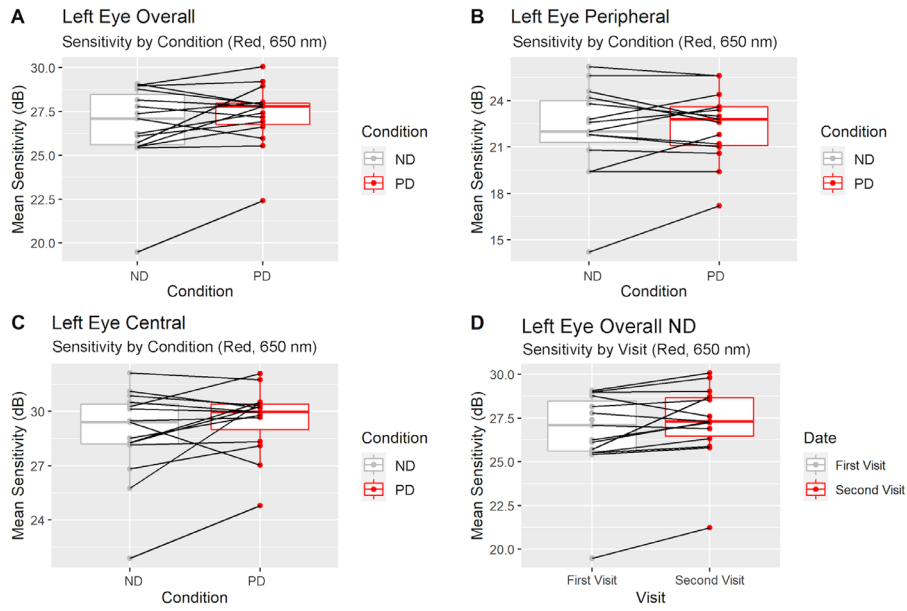
The residuals versus fits plot showed an even spread and no obvious trends. The random effects were also grossly normal. Finally, we checked a q-q plot of the residuals, which supported the assumption of normality. We checked for potential improvement with data transformations but found that none were superior to the identities. To account for alpha spending and to avoid false positives associated with repeated measures, a significance level of 0.01 was used given that we ran five models per color. Although we report *P* values, the focus of this article is on clinical significance as defined above. All statistical analyses were performed using R version 4.0.5 (R Core Team (2021); R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria).

## Results

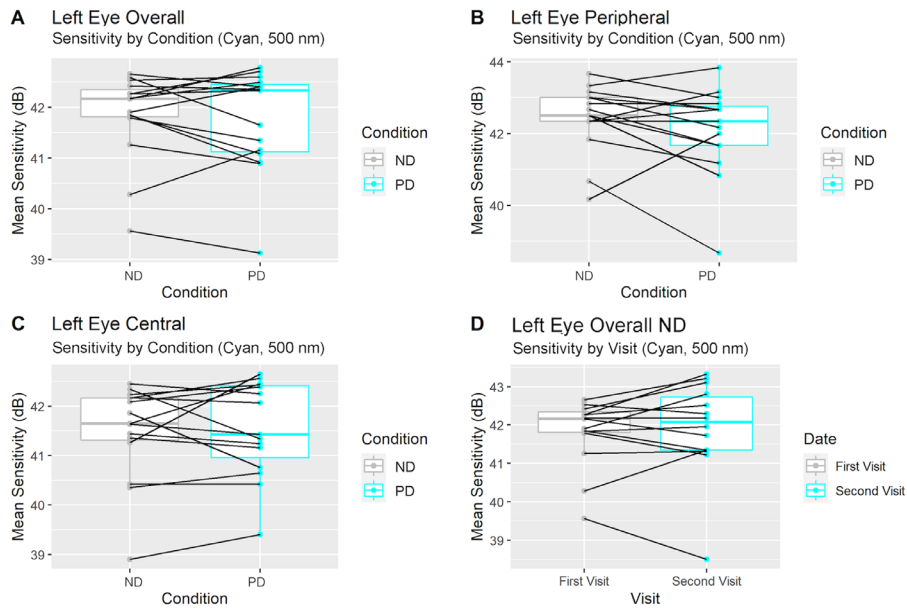
### Natural versus Pharmacological Dilation

Figures 1A and 2A compare the overall sensitivity of left eyes based on dilation status for red and cyan stimuli, respectively. Table 1 shows the results of the mixed effect models for the primary and secondary endpoints. The overall sensitivity was 0.54 dB higher under PD conditions compared to ND conditions for the red stimulus (95% confidence interval [CI], 0.05 dB to 1.03 dB). This was not clinically nor statistically significant at our alpha level of 0.01 ( $P = 0.032$ ). For the cyan stimulus, the overall sensitivity under PD conditions was 0.03 dB lower compared to the overall sensitivity under ND conditions (95% CI,  $-0.20$  dB to 0.15 dB). This was also not clinically nor statistically significant ( $P = 0.734$ ).

Figures 1B and 2B compare the peripheral sensitivity of left eyes based on dilation status for red and cyan stimuli respectively. The average sensitivity of peripheral points was 0.38 dB higher under PD conditions compared to ND conditions using the red stimulus (95% CI,  $-0.31$  dB to 1.07 dB). Using a linear mixed effect model, this was not clinically nor statistically significant ( $P = 0.277$ ). Our results showed the



**Figure 1.** Box plots comparing the sensitivity of individual left eyes to a red (650 nm) stimulus under varying situations. **(A)** Overall sensitivity by dilation status, **(B)** Peripheral sensitivity by dilation status, **(C)** Central sensitivity by dilation status, **(D)** Overall ND sensitivity by visit date. Boxes represent the twenty-fifth to seventy-fifth percentiles with the median denoted by the horizontal line within the box. Whiskers span all data points within 1.5 times the interquartile range of the twenty-fifth and seventy-fifth percentiles.



**Figure 2.** Box plots comparing the sensitivity of individual left eyes to a cyan (500 nm) stimulus under varying situations. **(A)** Overall sensitivity by dilation status, **(B)** Peripheral sensitivity by dilation status, **(C)** Central sensitivity by dilation status, **(D)** Overall ND sensitivity by visit date. Boxes represent the twenty-fifth to seventy-fifth percentiles with the median denoted by the horizontal line within the box. Whiskers span all data points within 1.5 times the interquartile range of the twenty-fifth and seventy-fifth percentiles.

average sensitivity of peripheral points using the cyan stimulus was 0.28 dB lower under PD testing vs ND testing (95% CI,  $-0.54$  dB to  $-0.01$  dB). This was not clinically nor statistically significant ( $P = 0.044$ ) (Table 1).

Figures 1C and 2C compare the central sensitivity of left eyes based on dilation status for red and cyan stimuli, respectively. Using a red stimulus, the average sensitivity of central points under the PD condition was 0.61 dB higher than the average sensitivity of

**Table 1.** Results From Simple Linear Mixed Effect Models

| Wavelength (nm) | Comparison  | Mean Effect Size (dB) | 95% CI (dB)    | P Value |
|-----------------|---|-----------------------|----------------|---------|
| Red (650)       | ND vs. PD (Overall)                                 | 0.54                  | 0.05 to 1.03   | 0.032   |
|                 | ND vs. PD (Peripheral)                              | 0.38                  | −0.31 to 1.07  | 0.277   |
|                 | ND vs. PD (Central)                                 | 0.61                  | −0.08 to 1.30  | 0.082   |
|                 | 1 <sup>st</sup> ND vs. 2 <sup>nd</sup> ND (Overall) | 0.45                  | 0.02 to 0.87   | 0.043   |
| Cyan (500)      | ND vs. PD (Overall)                                 | −0.03                 | −0.20 to 0.14  | 0.734   |
|                 | ND vs. PD (Peripheral)                              | −0.28                 | −0.54 to −0.01 | 0.044   |
|                 | ND vs. PD (Central)                                 | 0.12                  | −0.15 to 0.39  | 0.385   |
|                 | 1 <sup>st</sup> ND vs. 2 <sup>nd</sup> ND (Overall) | 0.11                  | −0.10 to 0.31  | 0.299   |

central points under the ND condition (95% CI, −0.08 dB to 1.30 dB). This was not clinically nor statistically significant ( $P = 0.082$ ). For the cyan stimulus, the average sensitivity of central points under the PD condition was 0.12 dB higher than the average sensitivity of central points under the ND condition (95% CI, −0.15 dB to 0.39 dB). This was not clinically nor statistically significant ( $P = 0.385$ ) (Table 1).

### ND Intertest Variability

Figures 1D and 2D compare the ND overall sensitivity of left eyes at the first visit vs the second visit for red and cyan stimuli respectively. The linear mixed effect model showed that the average overall sensitivity of the second ND test date was 0.45 dB higher than the first ND test date using the red stimulus (95% CI, 0.02 dB to 0.87 dB). This difference was neither clinically nor statistically significant at our significance level of 0.01 ( $p = 0.043$ ). For the cyan stimulus, the average overall sensitivity of the second ND test date was 0.11 dB higher than the first ND test date (95% CI, −0.10 dB to 0.31 dB). This difference was neither clinically nor statistically significant ( $P = 0.299$ ) (Table 1).

### Effect of Age

Using multiple linear mixed effect model to first control for dilation status demonstrated that overall sensitivity to red stimuli decreased by 0.77 dB per decade of increasing age (95% CI, −1.29 dB to −0.24 dB;  $P = 0.008$ ). When controlling for age, the sensitivity was 0.17 dB higher under PD conditions versus ND conditions for the red stimuli (95% CI, −1.29 dB to 1.64 dB;  $P = 0.813$ ), which was neither clinically nor statistically significant. For the red stimulus, the interaction between age and dilation was 0.09 dB (95% CI, −0.24

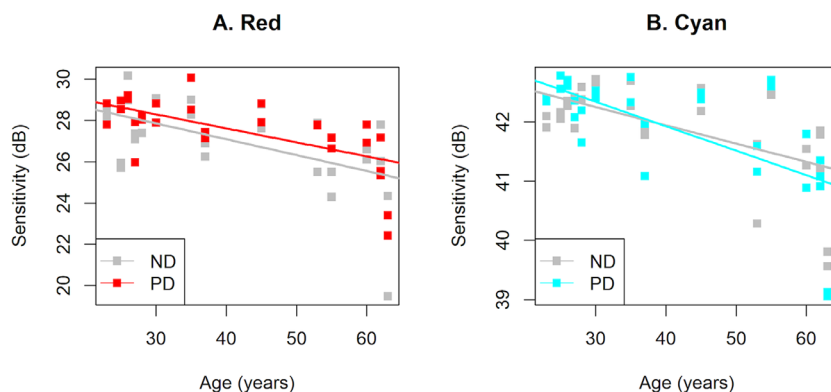
dB to 0.42 dB,  $P = 0.589$ ) which was neither statistically nor clinically significant.

When evaluating the cyan stimulus, the overall sensitivity decreased by 0.31 dB per decade of increasing age while controlling for dilation status (95% CI, −0.56 dB to −0.06 dB;  $P = 0.021$ ). When controlling for age, overall sensitivity was 0.40 dB higher under PD conditions versus ND conditions for the cyan stimuli (95% CI, −0.09 dB to 0.90 dB;  $P = 0.103$ ), which was neither clinically nor statistically significant. The interaction between age and dilation for the cyan stimulus was −0.10 dB (95% CI, −0.22 dB to 0.01 dB;  $P = 0.065$ ), which was neither clinically nor statistically significant. As age increases, the overall sensitivity decreases by 0.31 dB per decade when holding dilation status constant.

The decreases in sensitivity as age increases under PD conditions is not significantly different than the decrease under ND conditions for both stimuli. The changes in sensitivity based on age and dilation status are visualized in Figure 3. These results are summarized in Table 2.

## Discussion

Our testing showed no clinically meaningful differences in overall, central, or peripheral sensitivity based on dilation status in 2cDAP for both the red and cyan stimuli tested along the horizontal meridian. The effect size of the difference between overall sensitivity in same day ND versus PD testing was also similar to effect size of the difference between overall sensitivity between ND testing on different dates (0.54 dB vs. 0.45 dB and −0.03 dB vs. 0.11 dB for red and cyan, respectively). This further supports the conclusion that the differences based on dilation status are not clinically meaningful and are similar to the



**Figure 3.** Plots showing sensitivity based on age and dilation status. **(A)** Sensitivity based on age and dilation status for the red (650 nm) stimulus. Lines represent the regression under ND and PD conditions. **(B)** Sensitivity based on age and dilation status for the cyan (500 nm) stimulus. Lines represent the regression under ND and PD conditions.

**Table 2.** Results From Multiple Linear Mixed Effect Models Including Age Increase by Decade (Decade), Dilation Status With Natural Dilation as the Reference (Dilation), and the Interaction of Decade and Dilation (Decade\*Dilation)

| Wavelength (nm) | Predictor Variable | Mean Effect Size (dB) | 95% CI (dB)    | P Value |
|-----------------|--------------------|-----------------------|----------------|---------|
| Red (650)       | Decade             | -0.77                 | -1.29 to -0.24 | 0.008*  |
|                 | Dilation           | 0.17                  | -1.29 to 1.64  | 0.813   |
|                 | Decade*Dilation    | 0.09                  | -0.24 to 0.42  | 0.589   |
| Cyan (500)      | Decade             | -0.31                 | -0.56 to -0.06 | 0.021   |
|                 | Dilation           | 0.40                  | -0.09 to 0.90  | 0.103   |
|                 | Decade*Dilation    | -0.10                 | -0.22 to 0.01  | 0.065   |

\*Indicates significant *P* value at significance level set to 0.01 due to repeated measures.

day-to-day variability that are expected with psychophysical testing such as perimetry. Additionally, there were no statistically significant differences between same-day ND and PD overall, central, or peripheral testing using a significance level of 0.01. A previous study evaluating mesopic two-color microperimetry testing the central 10° of vision in both normal eyes and eyes with choroideremia also found no statistically significant difference based on dilation status.<sup>15</sup> Our study supports these findings and further suggests that this is true for scotopic perimetry and is not limited just to the macula.

In comparison, other studies have suggested that pharmacological pupil dilation results in significantly lower sensitivity in both normal and glaucomatous eyes undergoing photopic testing using Humphrey and Octopus perimeters; although the average decrease in normal eyes was small (~1 dB), they were still larger than our estimated effect sizes.<sup>12-14</sup> This difference may be attributed to the differences in the amount and

angle of light entering the pupil under scotopic versus photopic conditions, the Stiles-Crawford effect, and the effect of pupil dilation on centration and aberration. The Stiles-Crawford effect is a cone-mediated phenomenon that results in a lower quantal capture of photons from obliquely-angled light as compared to light rays parallel to the cones.<sup>18</sup> The directional sensitivity of cones can vary several-fold whereas the directional sensitivity of rods has minimal variation suggesting that rods show little difference in quantal capture photoreceptor response to oblique versus parallel light whereas cones do.<sup>19</sup> Increasing pupil diameter increases the amount of light that can enter the eye and therefore can increase sensitivity. However, there is an increase in aberrations and blur as pupil diameter increases given that the eye is not a perfect optical instrument and that pupil dilation results in pupil decentration.<sup>14,20</sup> Although changes in pupil diameter and therefore blur and aberrations are present under scotopic conditions, there is a greater

difference under photopic conditions that may help explain the differing results in our study versus the aforementioned photopic studies.<sup>12–14</sup>

Our results support previous findings that sensitivity decreases with increasing age and furthermore suggest that there is no significant interaction between age and dilation status in 2cDAP. While this decrease is not clinically significant for a single decade, over several decades the effect size becomes clinically significant. A recent study showed that sensitivity to a 505 nm wavelength stimulus using a dark adapted Medmont perimeter decreased with increasing age.<sup>6</sup> Additionally, a study evaluating the sensitivity to a 450 nm stimulus using a scotopic Humphrey Field Analyzer at points along the horizontal meridian showed that older subjects (mean age 70 years) had a lower sensitivity compared to younger subjects (mean age 27 years).<sup>17</sup> Our study supports these findings and suggests that this age-related decrease in sensitivity occurs with 500 nm and 650 nm stimuli, and the rate of decrease per decade is similar for both the PD and ND conditions.

The primary limitations of this study are the relatively small sample size of 29 eyes, the grid consisting of 16 points along the horizontal meridian instead of a 78-point full field grid, and the age range that did not include elderly patients which may be more affected by senile miosis. Additionally, this study did not address patients with AMD where rods are selectively affected.

These findings suggest that dilation status does not have a clinically meaningful association with sensitivity in subjects undergoing 2cDAP. Given that 2cDAP protocols commonly call for pharmacological dilation before testing, subjects may be undergoing unnecessary pharmacological dilation. Further exploration into the association of dilation status and sensitivity in subjects with various retinal pathologies such as choroideremia and retinitis pigmentosa is warranted to more fully understand the implications during 2cDAP testing.

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