



The Effects of Pupil Dilation on MAIA Microperimetry

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Original Article – Clinical Science

Effects of pupil dilation on MAIA microperimetry

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ABSTRACT

Background: MAIA microperimetry assesses macular sensitivity to projected point light sources and maps eye movements to assess fixation stability. While microperimetry is gaining prominence as an assessment tool in clinical and research settings, there is no consensus on whether it should be performed before or after pupil dilation. No studies to date have examined the effect of pupil dilation on results. The aim of this project was to elucidate the effect of pupil dilation on microperimetry outcomes.

Design: Prospective audit.

Participants: Twenty healthy patients from post-operative cataract clinic and ten patients with choroideremia to simulate a disease with peripheral visual field loss.

Methods: Subjects underwent 10-2 68 point field testing using the MAIA microperimeter on each eye. Subjects then underwent randomised dilation of one eye and the test was repeated in both eyes.

Main Outcome Measures: We compared changes in threshold sensitivity and fixation stability pre- and post-pupil dilation. The undilated eye was analysed for any learning or fatigue effect caused by test repetition.

Results: Dilation produced no significant effect on threshold sensitivity (dilation effect: -0.29 decibels (dB), $p=0.23$) or fixation stability in healthy controls or in choroideremia patients (dilation effect: $+0.08\log$ bivariate contour ellipse area (BCEA) $p = 0.14$). There was also no significant learning effect seen in the undilated eye, with no improvement in threshold sensitivity (order of eye testing: $+0.03\log$ BCEA, $p=0.71$).

Conclusions: In the clinical setting patients may be tested for 10 degree microperimetry with or without pupil dilation, as both scenarios yield consistent and interchangeable results.

Key Words: Dilation, microperimetry, retinal sensitivity, MAIA

INTRODUCTION

Microperimetry testing is now used by a growing number of studies as a highly sensitive measure of functional change in conditions as diverse as diabetic maculopathy, AMD, myopic CNV, early glaucoma and inherited macular dystrophies¹⁻⁹. A variety of microperimeters exist but all operate according to the same basic principles. A confocal infrared imaging system is used to image the retina and track eye movements. Threshold light stimuli varying in intensity displayed on a mesopic background are used to test the visual sensitivity of the central 10 degrees of the macula^{10,11}. It is able to map out small scotomas, assess changes in fixation stability, and identify general or specific areas of threshold change in different disease conditions¹²⁻¹⁴. However, though it is gaining increasing prominence in both research and clinical practice, there is currently no standard protocol on whether or not pupil dilation affects microperimetry.

It is well known that pupil dilation produces statistically significant declines in threshold sensitivities in automated peripheral field perimetry both in healthy controls^{8,15,16} and in patients with known field defects^{17,18}. Pupil dilation may therefore also theoretically affect microperimetry results by altering the total amount of light falling on the retina, through the Stiles-Crawford effect, or by affecting depth of focus. Currently, there is no data on how dilation influences sensitivities in microperimetry, and no recommendations exist on whether patients should be examined dilated or undilated. The MAIA microperimeter (Centervue, Padova, Italy) specifies only a minimum pupil size of 2.5mm¹⁹ and MP-1 system does not recommend a minimum pupil diameter. However, a review of studies using microperimetry findings as an outcome measure shows researchers tend to either test dilated subjects^{2,20-22} for convenience after OCT and examination, to recommend differing minimum pupil diameters for optimum results¹⁹ or fail to mention if dilation was involved^{13,23,24}.

To interpret functional data meaningfully it is important to know if dilation influences microperimetry outcomes. This will also aid with designing patient flow in both a

clinical and research setting. The aim of this project was to quantify the effect of pupil dilation on microperimetry in healthy controls and in disease states.

METHODS

Microperimetry was performed using a microperimeter with inbuilt confocal scanning laser ophthalmoscope and eye tracker (Macular Integrity Assessment – MAIA, Centervue, Padova, Italy) in 20 healthy patients in a clinical audit at the Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, UK. The patient inclusion criteria were for healthy adults aged over 18 years; best-corrected visual acuity of 6/9 Snellen or better in either eyes, no co-existing ocular pathology, neurological disease or previous ocular surgery (except uncomplicated cataract surgery). Healthy patients were selected from a post-operative cataract clinics and were included only if they were pseudophakic or assessed to have no lens opacity, even if they met the visual acuity criteria. This was to remove any confounding effect of eccentrically situated lens opacities producing focal changes in threshold sensitivities.

Additionally 10 patients with choroideremia were assessed pre- and post-dilation. Choroideremia is an X-linked retinal disease characterised by progressive centripetal retinal degeneration leading to severe restriction of peripheral visual field and reduced macular sensitivity. Microperimetry was performed on choroideremia patients to assess the effect of pupil dilation on a subpopulation with both peripheral field loss and macular abnormality. We postulated that any effect of pupil dilation on microperimetry performance due to light falling on peripheral retina should be reduced in this subpopulation. All 10 adult male patients with choroideremia had genetic confirmed mutations in the *CHM* gene, and underwent assessments as part of an ongoing gene therapy clinical trial (NCT01461213). Choroideremia causes poor night vision and preserved central visual acuity until late in the disease process. Therefore it is a good disease model to assess the impact of dilation on central sensitivity as the impact of changes in the peripheral retina or adaptation will be minimised.

All subjects were dark adapted under mesopic conditions (luminance <1 lux) for 20 minutes prior to microperimetry. "Microperimetry-naïve" subjects first underwent a supra-threshold 10-2 "learning" microperimetry test in both eyes. Subjects then underwent the first full microperimetry test with physiological pupils. This consisted of a 10-2 68 point (4-2 strategy) field, using a Goldman III sized stimulus on a 4 asb background, with a stimulus range of 0 to 36 dB. For consistency with standard operating procedures, the right eye was always tested first and left eye second. The subjects were then given a 5 minute break to reduce the effect of fatigue on performance. After the break, the 10 choroideremia patients had both eyes dilated with 1.0 % tropicamide and 2.5 % phenylephrine, while half (n = 10) of the control patients had the right eye dilated and the other half (n = 10) had the left eye dilated. The latter was intended to counter any potential bias related to the order of testing or learning effect. After another 20 minutes of dark adaptation, a second full microperimetry test was performed in both eyes using the follow-up function on the MAIA microperimeter in order to improve reliability with retesting the same points. All the choroideremia patients were experienced at performing microperimetry.

The primary outcome measure was the effect of mydriasis on microperimetry, defined by difference in average threshold sensitivity and fixation stability between baseline and repeat testing. We also examined individual threshold points for focal areas of change. The difference in threshold sensitivity between the baseline and repeat tests was calculated with a positive value indicating gain of sensitivity and negative value indicating loss of sensitivity. Differences in fixation stability as represented by the log 95% fixation area (represented by the bivariate contour ellipse area, or log BCEA) were calculated between the tests, with a positive value indicating a decrease in fixation stability and negative value indicating an increase in fixation stability. The measures recorded are shown in Figure 1.

We also undertook secondary data analyses to assess whether the effects of mydriasis on microperimetry were influenced by age, and whether the difference in performance between first and second eyes may be attributed to learning or fatigue.

Data was tested for normality using Shapiro-Wilk. We analysed 50 eyes of 30 patients using a basic linear mixed effects model with mydriasis, age, pathology status, and order of eye testing as fixed effects, and individual patients as an additional random effect. Normality testing was carried out in StatsDirect (Version 2.8.0, StatsDirect Ltd, Cheshire, UK) and linear modelling carried out using the linear mixed effects (lme) function from the non-linear mixed effects (nlme) package in RStudio (Version 1.0.44, supported by R version 3.2.2.) All data was found to be normally distributed.

RESULTS

The mean age of the healthy controls was 46.4 years (range 20-79) and the choroideremia patients 42.0 years (range 17 to 71). The healthy cohort further split into two groups by age: 10 subjects aged 20-28 years were taken as the 'younger cohort' and 10 aged 54-79 years were taken as the 'older cohort.' Snellen visual acuity ranged from 6/4 to 6/7.5 in the healthy cohort.

Figure 1 shows typical MAIA microperimetry results pre- and post-dilation, displaying the macular area assessed, fixation area and error, and threshold sensitivities. Figure 2 shows the impact of dilation on threshold in the different cohorts. A positive result indicates improvement on retesting whereas a negative result indicates a deterioration on retesting. Pupil dilation did not appear to have any significant effect on average threshold sensitivity in healthy controls or choroideremia patients. The mean threshold sensitivities of healthy undilated eye, healthy dilated eye and choroideremia dilated eye were 0.09dB, 0.20dB, and 0.02dB respectively. The effect of pupil dilation on threshold was -0.29dB (SE 0.29, $p = 0.23$). The effects of age (older patients: +0.15dB, SE 0.29, $p=0.61$), and severe visual field restriction (i.e. choroideremia: +0.15dB, SE 0.38, $p=0.69$) on threshold change were also insignificant. Order of eye testing (1st eye tested: +0.13dB, SE 0.32, $p=0.68$) was also insignificant, indicating lack of a learning or fatigue effect. Each point tested has a unique ID assigned to it by the MAIA microperimeter, and this is consistent across patients. Mapping of point-by-point thresholds revealed no qualitative focal

effect of dilation on threshold sensitivity (Figure 3a and b). Furthermore, comparison of dilation effect on threshold sensitivity of the centre 16 points of the 68 point field to the peripheral 52 points revealed no quantitative focal effect of dilation (threshold change in the centre compared to periphery: +0.10dB, SE 0.21dB, $p = 0.64$.) We chose the central 16 points as these subtend the central 8 degrees of the macula, corresponding to the anatomical location of the fovea and hence area of greatest sensitivity.

Dilation produced no significant effect on average fixation stability as measured by the log 95% BCEA (bivariate contour ellipse area, or 95% fixation area). The mean fixation area of healthy undilated eye, healthy dilated eye and choroideremia dilated eye were 0.00logBCEA, 0.08logBCEA, and 0.03logBCEA respectively (Figure 4). The overall effect of dilation on fixation area was +0.08logBCEA (SE 0.05, $p=0.14$). The effect of age (older patients: +0.05logBCEA, SE 0.07, $p=0.44$), severely restricted field (i.e. choroideremia: -0.08logBCEA, SE 0.08, $p=0.40$), and order of eye testing (+0.03logBCEA, SE 0.08, $p=0.71$) were also insignificant.

DISCUSSION

It is well known that pupil dilation lowers automated static field perimetry performance and threshold sensitivity^{8,15,17,18}. A number of proposed causes exist for this effect, including decreased depth of field leading to a defocusing effect after pupil dilation, and an increased impact of the Stiles-Crawford effect with a larger pupillary aperture permitting more peripheral light entry.

Automated field perimetry, however, differs from microperimetry in several key areas^{10,25,26}. While automated static perimeters such as the Humphrey (HFA) uses a projection system to project high luminance stimuli on a bright background (10 cd/m²) to measure both central and peripheral field up to 30 degrees, the MAIA microperimeter measures the central 10 degrees of vision in mesopic conditions (1.27 cd/m²). The MAIA therefore stimulates both rod and cone photoreceptors while the HFA stimulates mainly cones^{27,28}. The Humphrey field uses pupillary

reflexes to track fixation, while the MAIA uses confocal scanning laser technology to image the posterior pole in real time and hence both track fixation and present stimuli to the mapped area accounting for any eye movements. It is therefore by no means clear what effect, if any, pupillary dilation would have on MAIA performance.

Clarifying the effect of pupillary dilation on microperimetry performance is important as currently there is no consensus in the research community on whether pupillary dilation should be a pre-requisite for undergoing microperimetry testing. Studies may test patients dilated, undilated, or fail to clarify their dilation status^{13,20,29,14,2,21,23,24}. If pupillary dilation affects microperimetry performance, it would impede our ability to compare and interpret the results of studies examining patients with different dilation status. On the other hand, if dilation has no effect on performance, serial analysis and comparison between studies would be facilitated.

This study examines the effect of pupil dilation on macular threshold sensitivity and fixation stability as measured with the MAIA microperimeter in both healthy and in choroideremia patients. The MAIA operating protocol specifies that mydriasis is not required for operation provided a minimum pupil diameter of 2.5 mm is reached¹⁹. Our working hypothesis was that pupil dilation has no effect on microperimetry performance. We postulated that the mechanisms causing decreased performance in dilation in static automated perimetry would be insignificant due to the differences described above between static perimetry and microperimetry. As the MAIA maps the macula, it automatically brings its presented stimuli into focus for refractive error ranging from -15 D to +10 D¹⁹. This would theoretically eliminate defocussing and depth of field effects on threshold sensitivity. The Stiles-Crawford effect, which is so pronounced in perimetry examining the peripheral field, is an effect of oblique light entry which would be significantly decreased in microperimetry, in which light stimuli are projected through the large aperture of a mesopic-adapted pupil onto the central macula. Furthermore, the Stiles-Crawford effect is primarily a phenomenon produced by cone responses³⁰. Due to the mesopic conditions under which MAIA microperimetry is performed, a proportion of the perceptual response is rod-mediated²⁸ which would further decrease threshold changes caused by the Stiles-

Crawford effect. It was therefore notable that even in the cohort of choroideremia patients in whom rod function is known to be impaired, pupil dilation did not affect sensitivity of the central 10 degree field. Finally, though a pupil size smaller than the 2.5 mm specified by MAIA would affect threshold by mismatch of pupillary aperture with the MAIA viewing piece exit pupil, it is unlikely that a mesopic-adapted eye would fail to meet the required dilation in the natural state.

Our alternative hypothesis is that pupil dilation does influence microperimetry performance. There are a number of theoretical mechanisms to account for such a hypothesis. Dilation may decrease threshold by increased peripheral light scatter from increased total light entering the retina, leading to decreased contrast between a light stimulus and the overall luminance. Furthermore, although the Stiles-Crawford effect is reduced in microperimetry by the contribution of rod responses, it may still produce an effect. Dilation may also increase threshold and fixation stability by increasing light entry into a larger pupil, and thus improving macular mapping and imaging. For this reason we also included choroideremia patients and the absence of the gain in retinal sensitivity following dilation in this cohort of patients further confirms that the influence of having a larger pupil appears minimal in patients who have reduced central rod function.

Our results support the hypothesis that pupil dilation does not significantly influence microperimetry performance. We therefore conclude that patients may undergo microperimetry testing either dilated or undilated. This should improve clinic workflow as patients will be suitable for testing regardless of their dilation status. This would allow comparison of microperimetry results across studies whether or not subjects' dilation status is specified in the protocols.

Mesopic adaptation time is another variable which can influence microperimetry performance. For this study, we have followed the Oxford Eye Department's standard operating procedure for MAIA microperimetry, which requires 20 minutes of mesopic adaptation prior to testing. However, as with pupil dilation status, there exists a paucity of evidence surrounding the optimum mesopic adaptation time.

Further study is required on this aspect of microperimeter operation to inform future research and clinical protocols and allow for meaningful comparison between studies.

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For Peer Review

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FIGURE LEGENDS

Figure 1: Example of MAIA microperimetry results pre- and post-pupil dilation in a normal patient.

- A.** Pre-dilation MAIA microperimetry plot
- B.** Post-dilation MAIA microperimetry plot
- 1.** Macular image.
- 2.** Individual sensitivity threshold points with overlaid fixation plot.
- 3.** Sensitivity threshold map.
- 4.** Fixation area plot.
- 5.** Average threshold values.
- 6.** 63% and 95% fixation area values.

Figure 2: Threshold differences (dB) between baseline test and repeat test. There was no significant change in threshold differences (dB) across all five cohorts of eyes.

- Group 1= older healthy group undilated eye, n = 10
- Group 2= older healthy group dilated eye n = 10
- Group 3 = younger healthy group undilated eye n = 10
- Group 4 = younger healthy group dilated eye n = 10
- Group 5= Choroideremia group dilated eye n = 10

Figure 3a: Point by point threshold differences (dB) between baseline test and repeat test in the undilated eye (n=20) and the dilated eye (n=20) in the healthy group. Undilated eyes are indicated by the solid blue line with solid circle markers, and dilated eyes are indicated by the dashed orange line with empty square markers.

Figure 3b: Retinal map of average point by point threshold differences (dB) between baseline test and repeat test in the undilated eye (n=20) and the dilated eye (n=20) in the healthy group. Positive points (green) indicate an increase in threshold sensitivity and negative points (red) a decrease in threshold sensitivity.

Comparison of dilation effect on threshold sensitivity of the centre 16 points of the 68 point field to the peripheral 52 points revealed no quantitative focal effect of dilation (threshold change in the centre compared to periphery: +0.10dB, SE 0.21dB, $p = 0.64$.)

Figure 4: 95% fixation area logBCEA differences between baseline test and repeat test.

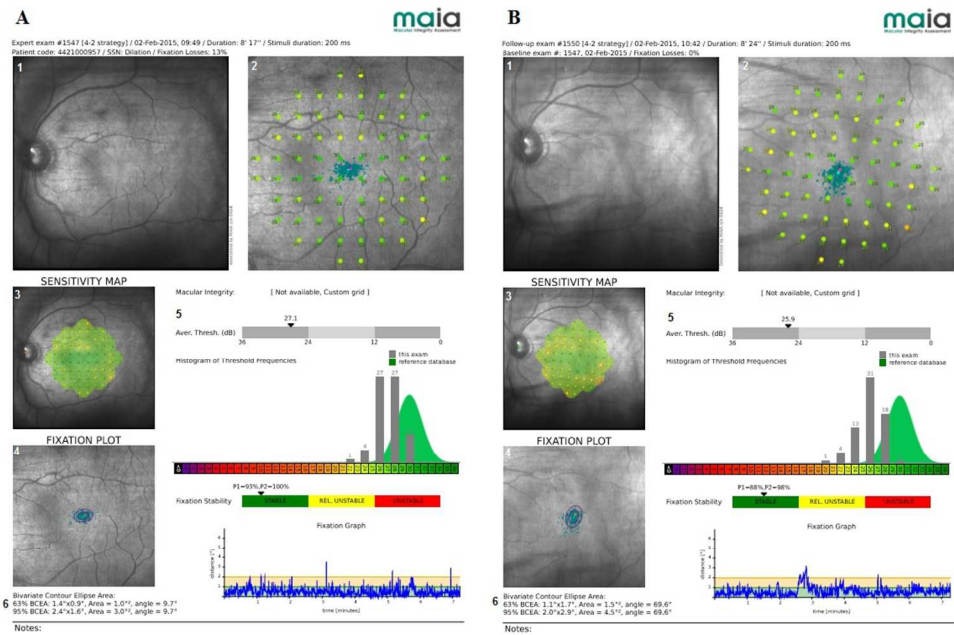
Group 1 = older healthy group undilated eye $n = 10$

Group 2 = older healthy group dilated eye $n = 10$

Group 3 = younger healthy group undilated eye $n = 10$

Group 4 = younger healthy group dilated eye $n = 10$

Group 5 = Choroideremia group dilated eye $n = 10$

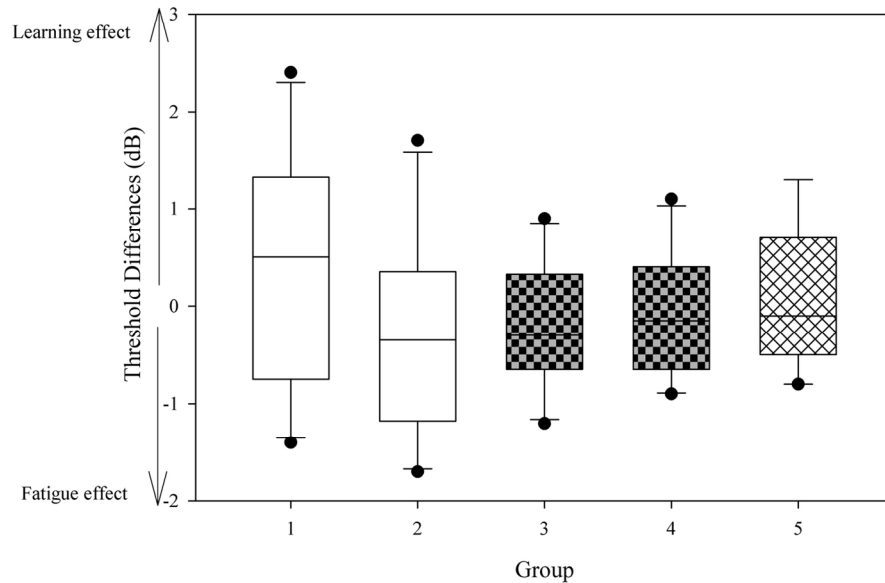


Example of MAIA microperimetry results pre- and post-pupil dilation in a normal patient.

- A. Pre-dilation MAIA microperimetry plot
- B. Post-dilation MAIA microperimetry plot
 - 1. Macular image.
 - 2. Individual sensitivity threshold points with overlaid fixation plot.
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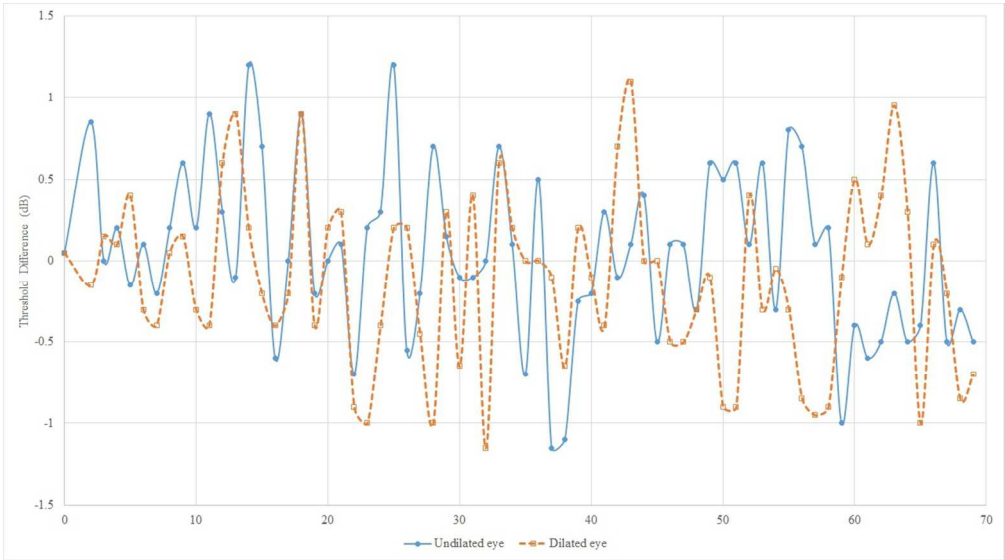
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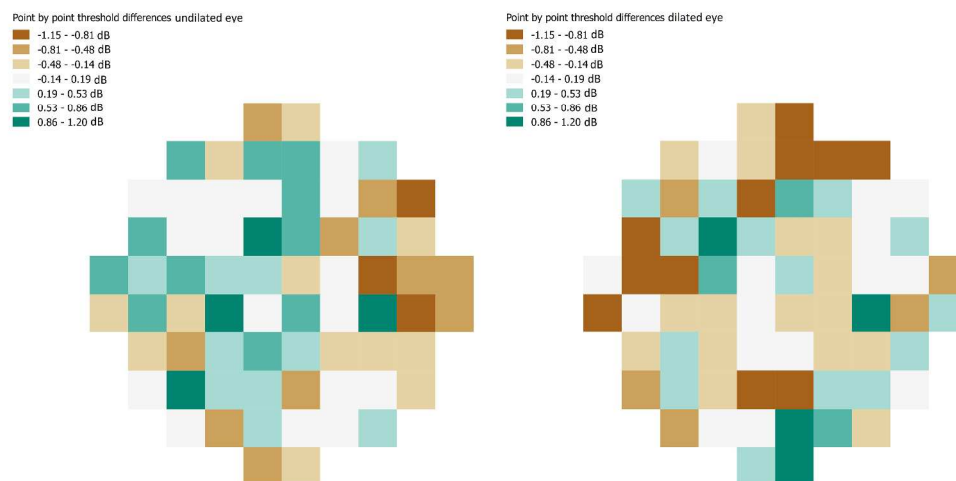
Threshold differences (dB) between baseline test and repeat test. There was no significant change in threshold differences (dB) across all five cohorts of eyes. !! + Group 1= older healthy group undilated eye, n=10!! + Group 2= older healthy group dilated eye n= 10!! + Group 3 = younger healthy group undilated eye n= 10!! + Group 4 = younger healthy group dilated eye n= 10!! + Group 5= Choroideremia group dilated eye n= 10!! +

132x95mm (300 x 300 DPI)



Point by point threshold differences (dB) between baseline test and repeat test in the undilated eye (n=20) and the dilated eye (n=20) in the healthy group. Undilated eyes are indicated by the solid blue line with solid circle markers, and dilated eyes are indicated by the dashed orange line with empty square markers.

337x188mm (96 x 96 DPI)



Retinal map of average point by point threshold differences (dB) between baseline test and repeat test in the undilated eye (n=20) and the dilated eye (n=20) in the healthy group. Positive points (green) indicate an increase in threshold sensitivity and negative points (red) a decrease in threshold sensitivity. Comparison of dilation effect on threshold sensitivity of the centre 16 points of the 68 point field to the peripheral 52 points revealed no quantitative focal effect of dilation (threshold change in the centre compared to periphery: +0.10dB, SE 0.21dB, $p = 0.64$.)

2065x1071mm (96 x 96 DPI)

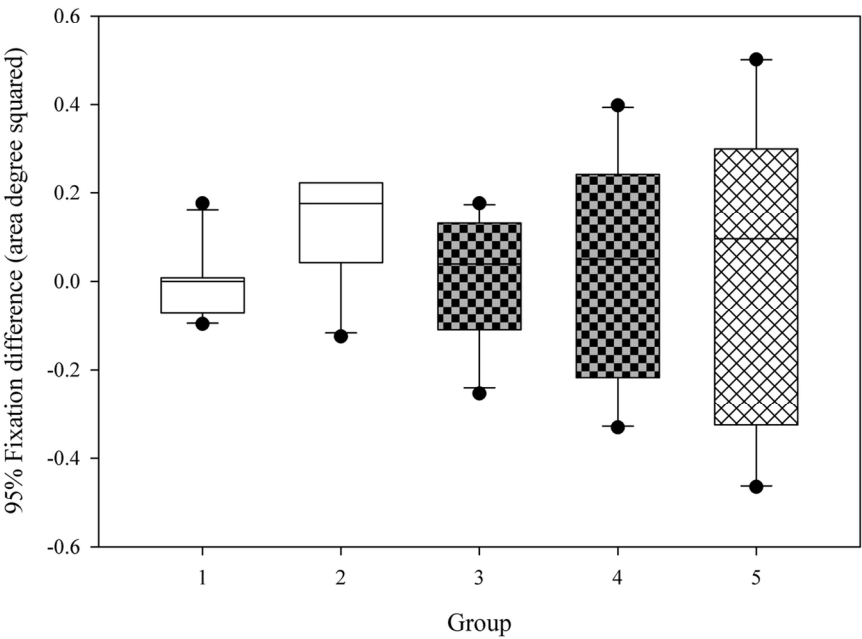


Figure 4. 95% fixation area logBCEA differences between baseline test and repeat test. There was no significant change in fixation area across all five cohorts of eyes.

- Group 1 = older healthy group undilated eye n = 10
- Group 2 = older healthy group dilated eye n = 10
- Group 3 = younger healthy group undilated eye n = 10
- Group 4 = younger healthy group dilated eye n = 10
- Group 5 = Choroideremia group dilated eye n = 10

127x97mm (300 x 300 DPI)

