Assessment of scotopic retinal sensitivity as a potential clinical trial end-point for rod-cone dystrophies

Anika Nanda[1,2*], Jasleen K. Jolly[1-3], Thomas M W Buckley[2], Holly Bridge DPhil[3], Robert E. MacLaren DPhil[1,2]

[1] Nuffield Laboratory of Ophthalmology, Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom, [2]Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom, [3]Oxford Centre for Functional MRI of the Brain (FMRIB), Wellcome Centre for Integrative Neuroimaging, University of Oxford, Oxford, United Kingdom, [4]Department of Ophthalmology, University of Bonn, Bonn, German, [5]Department of Biomedical Data Science, Stanford University, Stanford, USA

Introduction:

- In several rod-cone dystrophies the earliest symptom is often night blindness but there is currently no acceptable method of accurately quantifying dark adapted visual function. .
- The MAIA device has been updated and is now capable of performing scotopic testing in addition to mesopic testing, known as the S-MAIA (Centervue, Padova, Italy). It utilises cyan stimuli (505 nm) and red stimuli (627 nm) with the difference calculated between them.
- Cyan stimuli assess rod function and red stimuli assess cone function.
- In a normal patient, the expected cyan-red-sensitivity difference would be 0 dB given the employed scale (Pfau et al., 2017a).
- We aim to quantify scotopic function using the S-MAIA in mixed rod-cone dystrophies and mesopic microperimetry, thus evaluating whether S-MAIA is a viable clinical trial end point in patient with rod-cone dystrophies.

Methods:

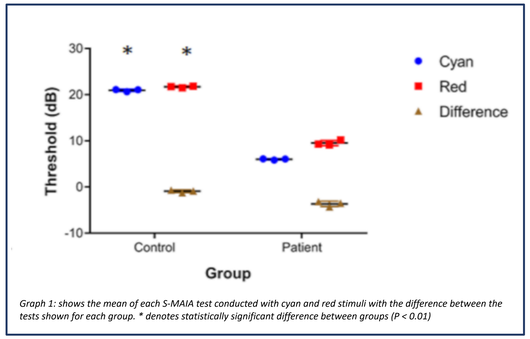
- Patients with a mixed diagnosis of rod-cone dystrophy and age and sex matched control patients underwent tests.
- Assessments included mesopic microperimetry and S-MAIA at 20 minutes (x3 tests) and 45 minute dark adaptation times.
- Testing was performed in the right eye only.
- Bland-Altman analysis was used to assess repeatability, and agreement between tests following the two time periods.

Measure	Patient eyes	Control eyes
Age (years)	47.7 [27 – 77]	48.0 [26 – 81]
Visual Acuity (letters)	78 [48 – 90]	84 [76 – 93]
Mesopic MAIA threshold (dB)	11.7 ± 9.3	26.6 ± 1.5
Scotopic cyan threshold (dB)	6.1 ± 7.5	21.1 ± 4.9
Scotopic red threshold (dB)	9.2 ± 6.7	21.8 ± 3.4
Difference between cyan and red (dB)	-3.2 ± 4.9	-1.2 ± 1.1

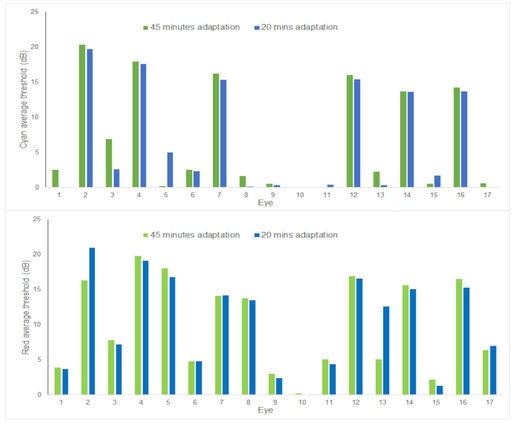
Table 1: Subject demographics and summary results of the participants completing the study.

Results

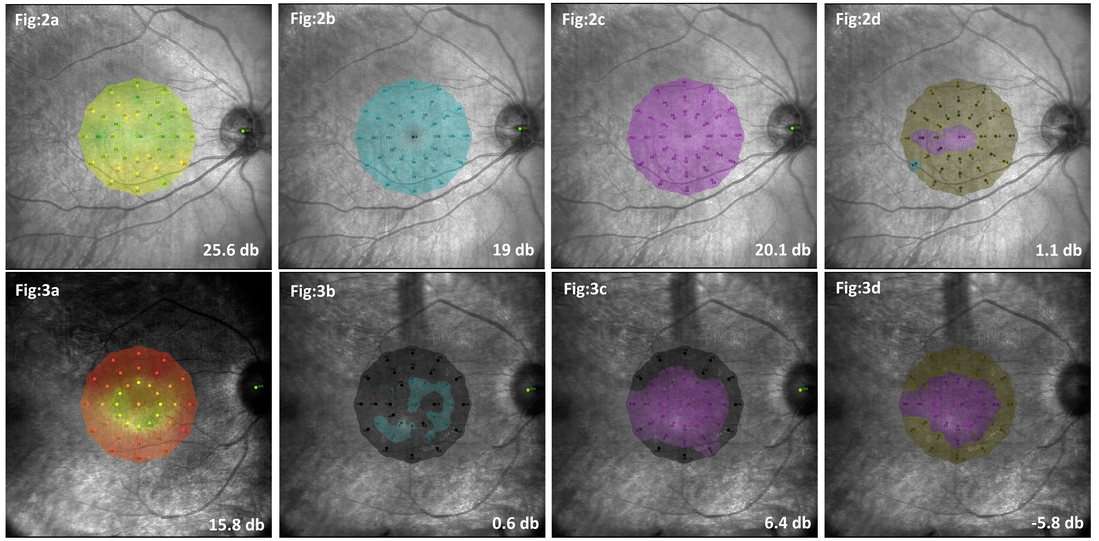
- Mesopic microperimetry, cyan and red stimuli thresholds (db) were all found to be statistically significant between participant and control groups ($p<0.01$)



*Graph 1: shows the mean of each S-MAIA test conducted with cyan and red stimuli with the difference between the tests shown for each group. * denotes statistically significant difference between groups (P < 0.01)*



Graph 2: Threshold measurements for each eye with cyan (top) and red (bottom stimuli comparing 45 minutes dark adaptation green bar) versus 20 minutes dark adaptation (blue bar). The mean difference between test 2 at 45 minutes and the test performed at 20 minutes was 0.5 dB for cyan and -0.3 dB for red.

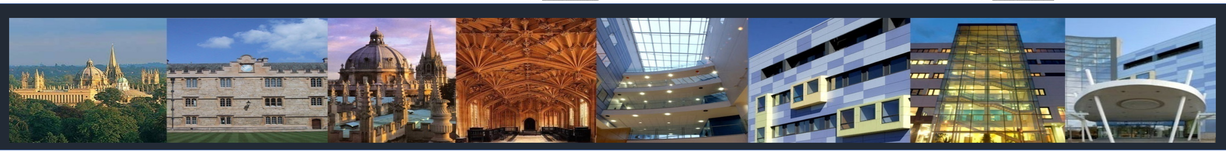


Figures 2 a-d & 3 a-d : Map of control (Figure 2) and patient (Figure 3) retinal sensitivity of mesopic (2a &3a), cyan and red tests in b & c with retinal sensitivity difference map in d. Mesopic retinal sensitivity is reduced in the patient (3a) compared to control (2a). Since the dark-adapted cone sensitivity is close to the rod sensitivity for the red long wavelength stimulus, isolated rod-dysfunction is characterized by a predominant loss of scotopic cyan sensitivity, resulting in negative cyan-red sensitivity differences (Heeren et al., 2019; Pfau et al., 2017b; Roman et al., 2005). Isolated rod dysfunction can be seen in 3b with the reduced retinal sensitivity of cyan S-MAIA test in comparison with 2b. The red test (2c & 3c) shows cone function/dysfunction. The negative difference in 3d compared to 2d shows a greater degree of rod dysfunction confirming the diagnosis of rod-cone retinal dystrophy. It is proposed that the greater the negative difference the greater the rod dysfunction.

CONCLUSION:

- S-MAIA can be a useful measure of scotopic function in rod=cone dystrophy patients with VA above 0.7 logMAR.
- Extended adaptation time beyond 20 mins does not provide additional benefit.
- A learning effect takes place between test 1 and test 2 but not subsequently.
- This presents a valuable outcome measure for gene therapy and interventional trials in the monitoring of disease.
- In the future, the S-MAIA could enable a specific disease course to be evaluated according to gene mutation to provide insights into disease mechanisms.

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Oxford Biomedical Research Centre

NHS National Institute for Health Research

Oxford University Hospitals NHS NHS Trust

Contact: anika.nanda2@nhs.net