Statistical Analysis Plan cover sheet

Wearable Dark-adaptometer in Normal Adult Healthy Volunteers

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WONDER STUDY
Evaluation of a novel wearable light-emitting system for measuring dark-adaptation thresholds in normal adult healthy volunteers

Statistical Analysis Plan

Chief Investigator: Rachel Williams
Principal Investigator: Alessandro Giuliano
Co-Investigator: Simon P. Harding
Collaborator: Noelia V. Pitrelli

Clinical Eye Research Centre, St Paul's Eye Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK
University of Liverpool, Department of Eye and Vision Science, Institute of Ageing and Chronic Disease, William Duncan Building, 6 West Derby Street, Liverpool, L7 8TX

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Cone- and rod-mediated dark adaptation functions were expressed as log threshold luminance vs. time (minutes). The dynamics of participants' visual recovery after the bleach offset were determined by fitting established models of human dark adaptation to collected threshold data. Two models were used: 1) a bi-exponential model, fitting a single exponential function separately to the cone-mediated phase and the rod-mediated phase of dark adaptation; and 2) an exponential bi-linear model, fitting a single exponential to the cone threshold recovery data and 2 linear components (i.e., S2 and S3) to any rod threshold recovery data.

1) $$D = \underbrace{\theta_1 + \theta_2 . \exp\left(\frac{-t}{\theta_3}\right)}_{\text{Cone}} + \underbrace{\eta_4 . \exp\left(\frac{-(t-\theta_5).h(t,\theta_5)}{\eta_6}\right)}_{\text{Rod}}$$

2) $$D = \underbrace{\theta_1 + \theta_2 . \exp\left(\frac{-t}{\theta_3}\right)}_{\text{Cone}} + \underbrace{\overbrace{\theta_4 . (t-\theta_5).h(t,\theta_5)}^{\text{S2}} + \overbrace{\theta_6 . (t-\theta_7).h(t,\theta_7)}^{\text{S3}}}_{\text{Rod}}$$

$$h(t,\pi) \begin{cases} 0 & \text{if } t-\pi \leq 0, \\ 1 & \text{if } t-\pi > 0. \end{cases} \qquad h(t,\pi) = \frac{1}{(1+e^{-k(t-\pi)})}$$

where θ_1 is the absolute cone threshold at time t after cessation of the bleach; θ_2 is the cone coefficient; θ_3 is the time constant of cone recovery referred to as cone τ; η_4 is the final rod threshold or rod absolute sensitivity; θ_4 is the slope of the second rod phase (S2), which represents the rate limited restoration of photopigment; θ_5 is the rod-cone transition time from bleach offset or α point; η_6 is the time constant of rod recovery; θ_6 is the slope of the final component (S3) of rod recovery; θ_7 denotes the time from bleach offset to the transition between the second and final components of rod recovery, referred to as β point; and h is a switch function as described.
Both models, respectively as in Eq. 1 and Eq. 2, have previously been shown to provide a suitable approximation of cone and rod photopigment regenerations after near total photopigment bleaches [1–3]. Matlab (The MathWorks, Natick, USA) was used to fit the dark adaptation models to collected data.

For the cone-mediated dark adaptation function, a single exponential fit was used to estimate the cone time constant (τ) and cone sensitivity parameters. The cone τ is the time constant of the exponential model and is an estimate of cone sensitivity recovery speed. The cone sensitivity is the plateau of the exponential function and is an estimate of the absolute threshold of cone photoreceptors.
For the rod-mediated dark adaptation function, the parameters of interest were the rod-cone break (RCB), rod slope, and rod sensitivity. The RCB is the time in minutes after bleach offset at which the rods are more sensitive to the test target than the cones. The rod slope is the slope of the sensitivity recovery during the second (S2) and third (S3) components of rod-mediated dark adaptation described by Lamb et al. [4,5]. The rod sensitivity parameter was measured as the minimum sensitivity value of the rod-mediated dark adaptation function around the 40 minutes end of the test.

Cone- and rod-mediated parameters were compared to previous literature on human dark adaptation to evaluate the performance of the developed dark adaptometer. Clinical data reported in [6] were particularly taken into consideration since a similar DA protocol was used by Jackson et al. to assess dark adaptation changes with age and as a function of decade. In addition, trial outcomes of interest were the test-retest and usability score results and variability obtained from participants after one or multiple DA visits.

Repeatability coefficient (RC) and within-case coefficient of variance (wCV) were calculated starting from the within-subject variance for each trial participant who completed at least 2 DA visits in order to assess variation in repeat measurements on the same patient. Intra-class correlation coefficient (ICC) – 2-way mixed-effects, absolute agreement, average measurement – was calculated for both

Group 1 and Group 2 through SPSS® Statistics V22.0 (IBM, Armonk, USA) to obtain the proportion of total variation in measurements by between-patient differences.

A pen-and-paper questionnaire as in Appendix 1-a was presented to participants twice on completion of the first and the third DA appointment. Seventeen questions targeting hardware and software implementation as well as personal feedback on the duration of the DA test were asked to rate comfort and ease of use of the developed system.

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