Measurement of cone dark adaptation: a comparison of four psychophysical methods

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Abstract

Purpose: Dark adaptometry is an important clinical tool for the diagnosis of a range of conditions, including age-related macular degeneration (AMD). In order to identify the most robust, clinically applicable technique for the measurement of cone dark adaptation, the repeatability and agreement of four psychophysical methods were assessed.

Methods: Data were obtained from 31 healthy adults on two occasions, using four psychophysical methods. Participants' pupils were dilated and 96% of cone photopigment was bleached before threshold was monitored in the dark using one of the techniques, selected at random. This procedure was repeated for each of the remaining methods.

An exponential recovery function was fitted to all threshold recovery data. The co-efficient of repeatability (CoR) was calculated to assess the repeatability of the methods and a repeated measures analysis of variance (ANOVA) was used to compare mean recovery parameters.

Results: All four methods demonstrated a similar level of inter-session repeatability for measurement of cone recovery, yielding CoRs between 1.18 and 1.56 minutes. There were no statistically significant differences in estimates of mean time constant of cone recovery (cone τ) between the four methods ($p = 0.488$), however significant differences initial and final cone thresholds were reported ($p < 0.005$).

Conclusions: All of the techniques were capable of monitoring the rapid changes in visual threshold that occur during cone dark adaptation and the repeatability of the techniques was similar. This indicates that, despite the respective advantages and disadvantages of these psychophysical techniques, all four methods would be suitable for measuring cone dark adaptation in clinical practice.

Key words

cone dark adaptation; repeatability; psychophysics

Introduction

For many decades the measurement of dark adaptation has played an important role in the detection and monitoring of a range of conditions including retinitis pigmentosa [1, 2], congenital stationary night blindness [3], Sorsby's fundus dystrophy [4, 5], vitamin A deficiency [5, 6], diabetic retinopathy [7, 8] and most recently, age-related macular degeneration (AMD) [9-15]. The clinical significance of dark adaptation measurement is growing because an emerging body of evidence suggests that it is a sensitive biomarker for AMD [9-18], the leading cause of visual impairment in the developed world [19, 20]. When measured alongside visual functions such as colour vision, flicker sensitivity, and photopic and scotopic thresholds, dark adaptation appears to be the single most sensitive marker for AMD [9-10, 15, 18]. Dark adaptometry is therefore an important clinical tool, however there is little published literature investigating the most robust psychophysical technique for the assessment of the change in visual threshold over time in the dark.

Cone dark adaptation is particularly attractive to clinicians because of its sensitivity to early AMD [10, 13-15] and the relative speed with which it can be recorded. However, the fundamental difficulty associated with measuring visual thresholds during dark adaptation is the speed with which threshold changes. This is particularly problematic when monitoring cone adaptation, in which the threshold decreases by approximately 2 log units during the initial 10 minutes in the dark [21, 22]. Clearly, rapid psychophysical methods capable of obtaining robust and repeatable threshold measurements are desirable.

Dark adaptation functions have often been recorded using custom made dark adaptometers [23-27]. However, several dark adaptometers are now commercially available, including LKC Technologies' SST-1 [28, 29] and MacuLogix's AdaptDx [30]. Given the increasing prevalence of age-related conditions such as AMD [31], the enhanced availability of effective treatments [32, 33], and the growing body of evidence that dark adaptation is a diagnostic tool in these conditions, it seems likely that the range of dark adaptometers will continue to expand.

The Goldmann-Weekers adaptometer, which is no longer commercially available, was considered the 'gold standard' method of measuring dark adaptation for many

decades. It used an operator controlled ‘method of ascending limits’ to determine the visual threshold and each threshold measurement was recorded directly onto logarithmic paper [34]. The ‘method of ascending limits’ has also been implemented in other dark adaptometers, using either simple computer controlled staircases, similar to those used in visual field equipment [9, 12, 27, 30], or adaptive staircases, which estimate threshold by fitting psychometric functions to a series of threshold estimates, in order to minimise redundant presentations and thus to improve the efficiency of testing [26, 35].

Although the psychophysical method of ascending limits is fast, it is prone to errors that may result from changes in the observer’s criterion [36], and in the case of the Goldmann-Weekers adaptometer, changes in the performance of the person operating the device. While adaptive techniques allow increasingly robust measurement of dark adaptation, they are still not entirely free from the effects of changes in the observer’s criterion. In this respect, forced choice methods are preferable, however they tend to be time consuming and have not, thus far, been used to track threshold during dark adaptation. In a forced choice procedure the observer is required to select one of a number of presented options on every trial. In the absence of response bias, the observer should select the option that contains the largest sensory signal [37].

In order to identify the most robust, clinically applicable technique for the measurement of visual threshold during cone dark adaptation, the repeatability and agreement of three computer based methods and the Goldmann-Weekers adaptometer were assessed. The computer based methods evaluated were: a hybrid adaptive stimulus presentation combined with a maximum likelihood calculation [26], a modified staircase procedure based on a method previously used with the Humphrey Visual Field Analyser [27] and a novel 10-alternative forced choice procedure. At the outset the hypothesis was that the repeatability of the data obtained using the Goldmann-Weekers adaptometer would be inferior to that obtained using the computer based techniques because operator error would introduce an additional source of variability into threshold measurements. In addition, it was hypothesised that the estimates of final cone threshold would be lower for the 10-alternative forced choice and hybrid adaptive techniques than for the method of ascending limits because these techniques should provide a genuine estimate of the observer’s

threshold [26, 38]. And finally, that there would be no significant difference in the rate of cone recovery between techniques because cone recovery should be independent of any translation of the data up or down the vertical axis and, to some extent, differences in variability between techniques.

Methods

Subjects

Thirty-one healthy adults, aged 20-31 years (mean age 21.6 +/- 2.5 years) were recruited. All participants had a corrected visual acuity of 6/6 or better in the test eye, clear ocular media, normal retinal appearance and no history of ocular or systemic disease. The study was approved by the Research Ethics Committee at the School of Optometry and Vision Sciences, Cardiff University and all procedures adhered to the tenets of the Declaration of Helsinki. All participants provided informed written consent prior to participation.

Experimental procedure

Participants attended the laboratory on two days within a two week period. At each visit, subjects' pupils were dilated with one drop of 1.0% Tropicamide in each eye. Dark adaptation was monitored monocularly and refractive correction was worn if required.

At the start of each session the procedures involved were explained to participants and a 5 minute familiarisation period was provided. This was extended until the investigator considered the subject to be competent with the procedure.

A Maxwellian view optical system was used to deliver a 96% bleach (5.78 log phot.Td for 60s) of cone photopigment [22] to the central 43.6º of the test eye. Upon cessation of the bleach, cone dark adaptation was monitored for 5 minutes, in response to a 4º diameter achromatic stimulus centred on the fovea, using one of four psychophysical techniques, selected at random. This procedure was repeated for each of the remaining psychophysical methods. A wash out period of 10 minutes was interleaved between successive bleaches to avoid carry-over effects.

Psychophysical methods

The Goldmann-Weekers adaptometer employed the method of ascending limits to record the dark adaptation function directly onto logarithmic paper. The investigator manually increased the intensity of the 4º diameter spot stimulus until the participant reported that it was just seen. Threshold was recorded by marking the recording paper, before the stimulus intensity was reduced and the procedure repeated. This continued throughout the recording period. Subsequently, the marks on the recording paper were digitised (DigitizeIt Ver 1.5) and transferred to a spreadsheet for analysis.

All other psychophysical procedures were computer based and all stimuli were presented on a calibrated, high resolution CRT monitor (Iiyama LS 902UT) driven by an 8-bit (nVIDIA Geforce 9) graphics board under software control (Matlab). The luminance output of the monitor was γ-corrected [39, 40] and modified by neutral density filters mounted on the screen to expose the full range of recovery. The background luminance of the CRT (-0.85 log cd/m²) was attenuated by a 1.2 ND filter in place throughout recordings. When the computer signalled that the lower end of the luminance range was approaching, additional filters were added to keep the monitor working within its linear range when necessary.

The stimulus was presented at the centre of the CRT, indicated by four fixation markers (Figure 1). Two of the methods used spot stimuli, whilst numeric stimuli were presented during the forced choice paradigm. The participant was instructed to fixate the centre of the screen and to indicate perception of the stimulus via the computer keyboard, or to report the number seen, in the case of the forced choice program.

Figure 1 about here

The hybrid adaptive procedure has been described by Friedburg et al. (1998) [26]. The target luminance on each trial was determined by a set of three decision criteria, based on the participant's previous responses (Table 1). An estimate of visual threshold was recorded when a maximum of twelve trials were exceeded or five consecutive reversals ('seen' to 'not seen') occurred. A maximum-likelihood computation was employed to determine threshold on the basis of the distribution of all of the subject's previous responses [35].

Table 1 about here

The modified staircase procedure was based on a method previously implemented using a Humphrey perimeter [27]. Stimuli were presented for 200 msec, followed by a 600 msec response window and then a randomly determined interstimulus delay of 0.9-2.4 seconds. If the participant reported perception of the stimulus within the response window, the luminance was reduced by 0.3 log units for the next presentation. Conversely, if the participant responded to the stimulus outside of the response window, or failed to respond at all, the intensity was increased by 0.1 log units on each of the following presentations. Threshold was recorded when the stimulus first became visible on an ascending staircase.

The 10-alternative forced choice program presented numeric stimuli, from zero to nine, within the central 4° field. Participants were instructed to report the number seen after every stimulus presentation, regardless of their level of confidence, and the investigator entered the response via the computer keyboard. For each correct response the luminance at the subsequent presentation was reduced by 0.3 log units and for each incorrect response it was increased by 0.1 log units.

Statistical analysis

The rate of cone recovery was determined by fitting an exponential model of dark adaptation to the cone threshold recovery data (Equation 1) [41]. An exponential model has previously been shown to provide a suitable approximation of cone photopigment regeneration after near total photopigment bleaches [42].

$$T(t) = a + (b * \exp^{(-t/\tau)}) \qquad \textit{Equation 1.}$$

where T is the threshold (log cd/m^2) at time t after cessation of the bleach, a is the final cone threshold, b is the change in cone threshold from t = 0 and τ is the time constant of cone recovery. The initial cone threshold was calculated as the sum of parameters a and b.

The repeatability of the four methods was assessed by evaluating the data from each of the visits using established statistical techniques [43], including by calculating the coefficient of repeatability (CoR). A repeated measures analysis of variance (ANOVA) was then used to compare the mean cone τ, initial and final cone thresholds obtained using the four psychophysical methods. A posthoc analysis (including Bonferroni correction) was used to determine which techniques differed significantly from each other.

Results

Cone dark adaptation functions were recorded from all 31 participants, using each of the methods described, on both occasions. Dark adaptation functions recorded from a typical participant (JF) at the first visit are shown in Figure 2. Threshold estimates were obtained approximately every 15 seconds using the hybrid adaptive procedure, approximately every 10 seconds using the Goldmann-Weekers adaptometer and 10-alternative forced choice procedures and approximately every 7 seconds using the modified staircase procedure.

Figure 2 about here

The mean (+/- standard deviation) cone τ, initial cone threshold and final cone threshold for each of the psychophysical methods are shown in Table 2. There were no statistically significant differences in mean cone τ between the four methods of dark adaptation measurement ($p = 0.488$). However, a significant difference was evident in the initial cone threshold estimates generated by the four methods ($p < 0.005$). Post-hoc analysis revealed that the initial threshold given by the Goldmann-Weekers adaptometer was significantly lower than those produced by the computer based techniques. In addition, there was a significant difference in the final cone threshold measured by the four methods ($p < 0.005$). More specifically, post-hoc analysis showed that the final cone threshold given by the Goldmann-Weekers adaptometer was significantly higher than that obtained using the hybrid adaptive procedure and 10-alternative forced choice methods.

Table 2 about here

The difference between the cone τ recorded at visit one and visit two is plotted as a function of mean cone τ for each psychophysical method, with the 95% limits of agreement, in the Bland-Altman plots shown in Figure 3. In each plot, the solid horizontal line describes the bias i.e. the absolute difference observed between visits, and the dashed lines the limits of agreement i.e. the coefficient of repeatability (CoR), calculated as two standard deviations above and below the bias line. All four psychophysical methods demonstrated a similar level of inter-session repeatability for measurement of cone dark adaptation, with overlapping 95% confidence intervals for the CoR. The data from one subject was excluded from all analyses as the mean cone τ obtained for this subject using the hybrid adaptive procedure fell beyond three standard deviations from the mean for that psychophysical method.

Figure 3 about here

There were no statistically significant differences in mean cone τ recorded at the first and second visits for any of the psychophysical methods studied ($p > 0.05$). Similarly, assessment of the order in which each psychophysical method was used within a single recording session showed no statistically significant differences in cone τ for test order (all $p > 0.05$). This analysis indicates that there were no learning, fatigue or bleach carry-over effects within the dataset.

Discussion

The major challenge encountered when monitoring cone dark adaptation is that of obtaining robust visual threshold estimates in the limited timeframe imposed by the rapid rate at which threshold changes. All four of the techniques used in this study were capable of monitoring the rapid changes in visual threshold that occurred during cone dark adaptation. The repeatability of the four methods was very similar, all yielding co-efficients of repeatability in the range of 1.18 to 1.56 minutes.

Assessment of the CoR is important when a technique is evaluated for clinical use as it indicates the extent of inherent variability, and so the smallest change which may be considered clinically significant. Therefore, for the methods evaluated here, a change of more than 1.18 - 1.56 minutes in cone τ between visits can be considered clinically

significant. A recent study that compared cone recovery within the central retina in a group of people with early AMD to a group of age-matched controls, using a similar computer based psychophysical technique, reported differences of 2.85-8.01 minutes in mean cone τ between the groups [16]. Clearly this difference is markedly greater than the CoRs reported here, suggesting that the psychophysical methods are capable of producing results which can reliably distinguish those with early AMD from healthy controls.

The CoR obtained for cone τ measured using the Goldmann-Weekers adaptometer in this study (1.18 +/- 0.22 minutes) is consistent with previous reports [44]. Contrary to expectations, the repeatability of the Goldmann-Weekers adaptometer was similar to that of the computer based methods, despite the fact that, unlike the computer based methods, the stimuli presented by the Goldmann-Weekers adaptometer are controlled by an operator i.e. they control stimulus intensity by manipulating a neutral density wedge. It is important to acknowledge that the investigator that carried out the recordings was highly trained in the operation of the Goldmann-Weekers adaptometer and therefore the CoR reported here was based on data obtained under optimal recording conditions. Consequently, the repeatability of the device may be poorer for a less experienced operator.

As expected, the lowest estimates of final cone threshold were generated by the hybrid adaptive and 10-alternative forced choice methods. The hybrid adaptive procedure was originally developed in response to the increasing demand for fully automated methods of dark adaptation measurement that could minimise the effects of subjective bias on the data [26]. When the technique was originally described, it was shown to produce lower final threshold estimates than the ascending staircase procedure employed by the Goldmann-Weekers adaptometer [26], a finding that was replicated in the current dataset. However, with regard to the repeatability of cone τ, the hybrid adaptive procedure had no advantage over the other techniques.

Forced choice methods have previously been shown to produce lower and more accurate threshold estimates compared to unforced subjective procedures because the measurements are criterion free [38]. As predicted, the 10-alternative forced choice method used here generated a significantly lower mean final threshold relative to that

attained with the Goldmann-Weekers adaptometer, but it was not significantly different to the other computer based methods. However, it is not really appropriate to make a direct comparison between the forced choice procedure and the other methods because this technique employed numeric stimuli, a more demanding identification task compared to the detection of the spot stimuli used by the other methods.

The initial cone threshold measured with the Goldmann-Weekers adaptometer was significantly lower than the initial cone thresholds generated by the computer based techniques. This could be explained by differences in the luminance range of the different techniques. The maximum stimulus intensity that the Goldmann-Weekers adaptometer can present is 0.4 log cd/m², compared to the maximum stimulus intensity of 0.8 log cd/m² presented by the computer. Consequently, when the computer methods were used, a greater number of data points were obtained during the earliest stages of dark adaptation to anchor the exponential model fit. Removal of the early data points generated by the computer based methods reduces this difference in the initial threshold between the techniques.

In summary, the performance of the Goldmann-Weekers adaptometer was compared to three computer based methods of measuring cone dark adaptation and the mean cone τ and CoR for each were reported. As expected the time constant of cone recovery was not significantly different between the techniques. However, contrary to expectations, there were no significant differences in the repeatability of the four techniques. Despite the theoretical advantages of the criterion free alternative forced choice and hybrid adaptive procedures, these results indicate that any of these psychophysical techniques may be used to measure cone dark adaptation in clinical practice.

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Figure legends

Fig. 1 CRT display used by the computer based dark adaptation procedures, set at a viewing distance of 55cm. Participants were instructed to fixate the centre of the screen indicated by four 1º x 0.5º fixation markers (a), where a 4º diameter achromatic stimulus was presented (b)

Fig. 2 Cone dark adaptation functions for participant JF, recorded at visit 1, using: the Goldmann-Weekers adaptometer (a), the hybrid adaptive procedure (b), the modified staircase procedure (c) and a novel 10-alternative forced choice procedure (d). Each plot is shown with the time constant of recovery (τ), the final cone threshold (a), the initial cone threshold (a+b) and a goodness of fit statistic (R^2).

Fig 3 Difference between cone τ recorded at visit 1 and visit 2 plotted as a function of mean cone τ, shown with the 95% limits of agreement for each psychophysical method: the Goldmann-Weekers adaptometer (a), the hybrid adaptive procedure (b), the modified staircase procedure (c) and a novel 10-alternative forced choice procedure (d). The coefficient of repeatability (CoR) for each technique is displayed in minutes. The open symbol in plot b indicates an outlying data point (3 standard deviations from the mean) from the participant that was excluded from all analyses

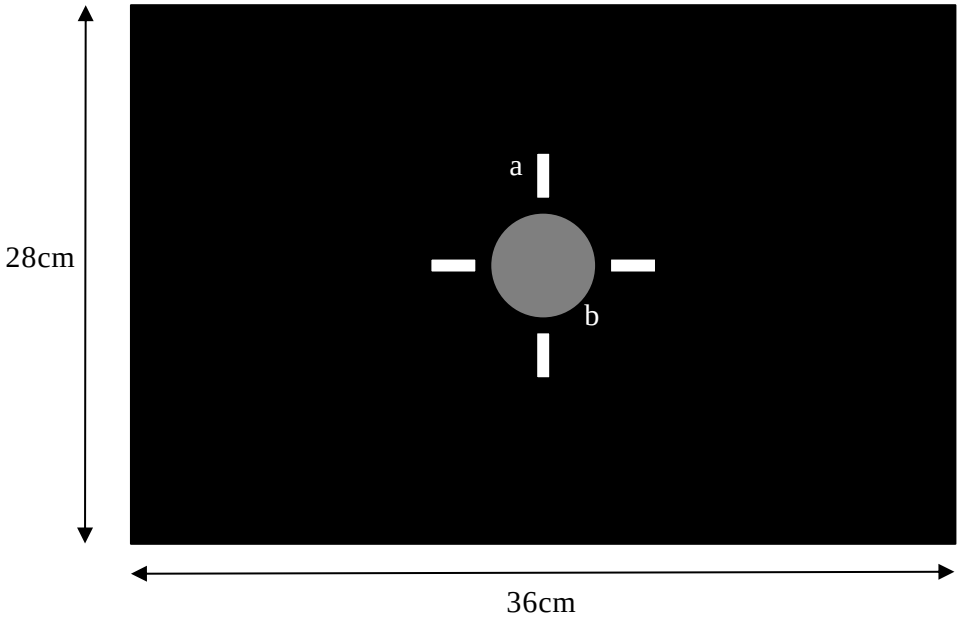
Tables

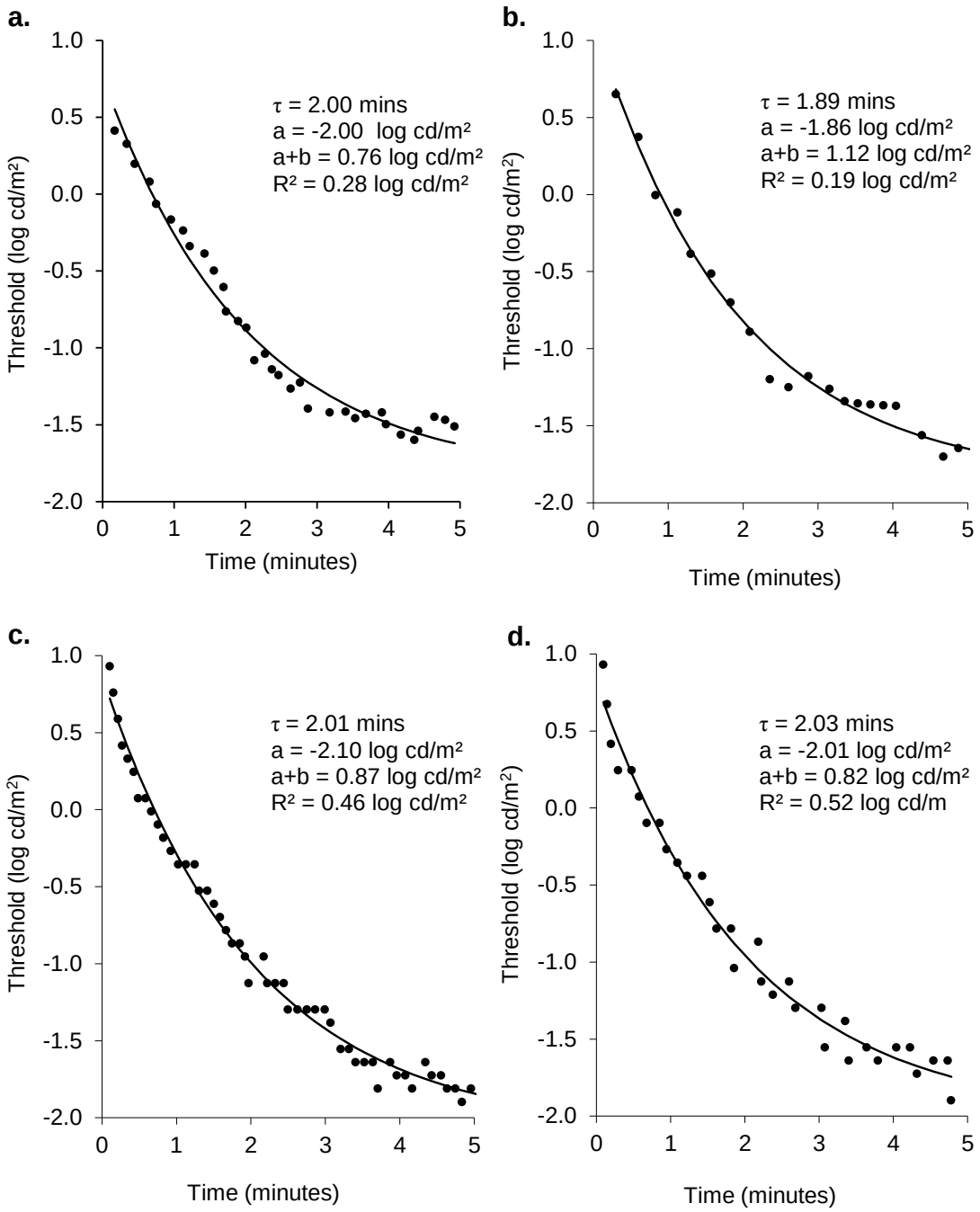
Table 1. Decision criteria used to determine target luminance by the hybrid adaptive psychophysical procedure [24].

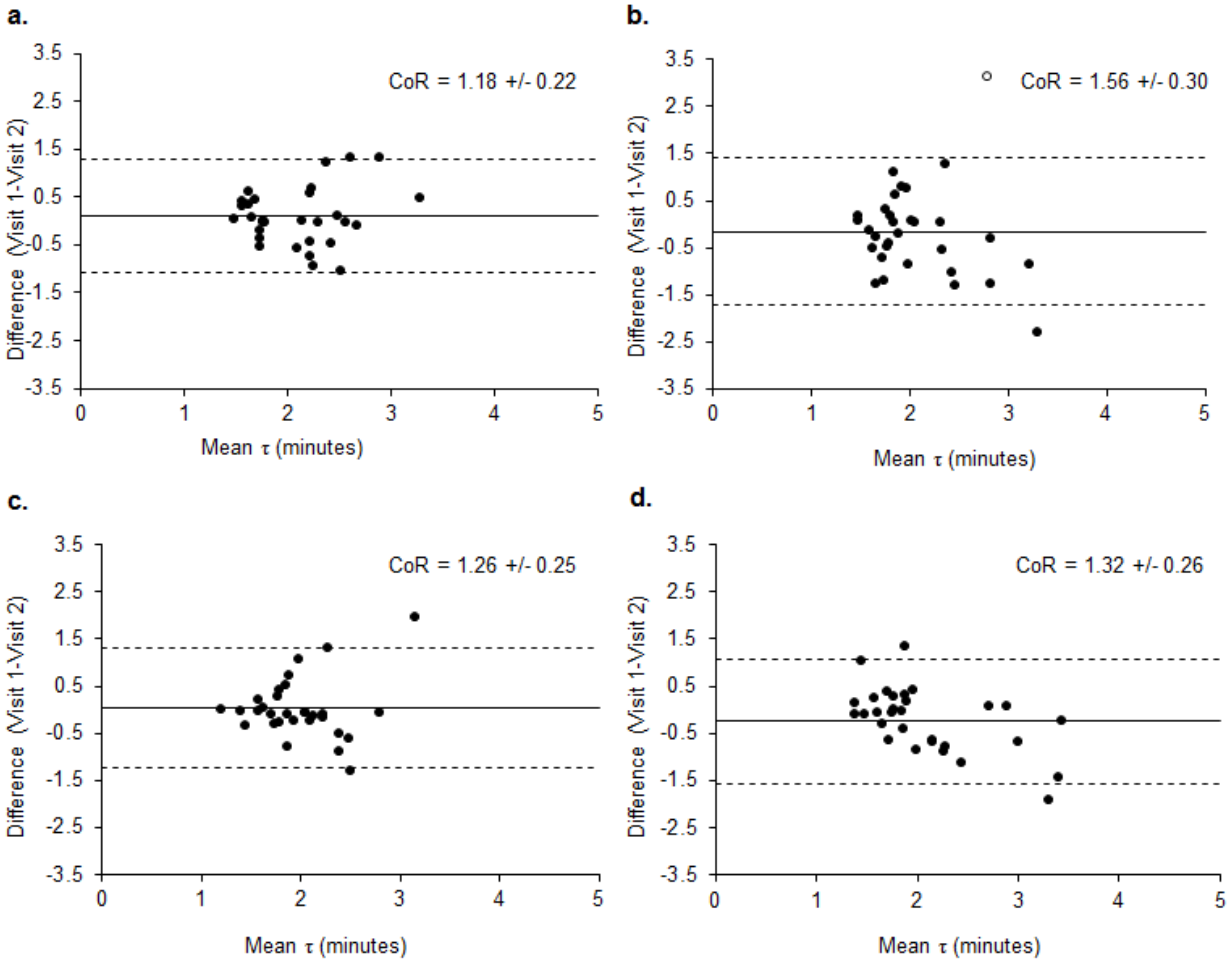
Response sequence	Target luminance
Response 'changes from 'seen' to 'not seen' or vice versa	Reversal of step direction and step size reduced by 60%
Response consistent for 2 trials	Step size and direction remain unchanged
Response consistent for 3 trials	Step size doubled but step direction remains unchanged

Table 2. Mean cone τ, initial cone threshold and final cone threshold for all subjects at visit 1 and visit 2 for the four psychophysical methods of dark adaptation measurement, where initial cone threshold is given by 'a+b', and final cone threshold is 'a' (Equation1).

	Goldmann-Weekers adaptometer	Hybrid adaptive procedure	Modified staircase procedure	10-alternative forced choice procedure	p-value
Cone τ (minutes)	2.11 (0.45)	2.05 (0.48)	1.99 (0.42)	2.09 (0.160)	= 0.488
Initial threshold (log cd/m²)	0.67 (0.12)	0.89 (0.21)	0.82 (0.16)	0.80 (0.15)	< 0.005
Final threshold (log cd/m²)	-1.81 (0.21)	-2.13 (0.33)	-2.05 (0.62)	-2.20 (0.33)	< 0.005


28cm
a
b
36cm


a.
τ = 2.00 mins
a = -2.00 log cd/m²
a+b = 0.76 log cd/m²
R² = 0.28 log cd/m²
Threshold (log cd/m²)
Time (minutes)
b.
τ = 1.89 mins
a = -1.86 log cd/m²
a+b = 1.12 log cd/m²
R² = 0.19 log cd/m²
Threshold (log cd/m²)
Time (minutes)
c.
τ = 2.01 mins
a = -2.10 log cd/m²
a+b = 0.87 log cd/m²
R² = 0.46 log cd/m²
Threshold (log cd/m²)
Time (minutes)
d.
τ = 2.03 mins
a = -2.01 log cd/m²
a+b = 0.82 log cd/m²
R² = 0.52 log cd/m
Threshold (log cd/m²)
Time (minutes)


a.
CoR = 1.18 +/- 0.22
Difference (Visit 1-Visit 2)
Mean τ (minutes)
b.
CoR = 1.56 +/- 0.30
Difference (Visit 1-Visit 2)
Mean τ (minutes)
c.
CoR = 1.26 +/- 0.25
Difference (Visit 1-Visit 2)
Mean τ (minutes)
d.
CoR = 1.32 +/- 0.26
Difference (Visit 1-Visit 2)
Mean τ (minutes)