Adaptive Changes in Color Vision from Long-Term Filter Usage in Anomalous but Not Normal Trichromacy

Highlights
- Long-term use of color notch filters increases chromatic response in color anomals
- No such effects are observed in normal trichromats or a placebo condition
- Spontaneous comments of observers suggest that the effects may endure

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In Brief
Werner et al. report that extended usage of a spectral notch filter boosts chromatic response in individuals with the most common forms of red-green color deficiency (anomalous trichromacies). The measured effects are supported by spontaneous comments and persist even after removal of the filters.
Adaptive Changes in Color Vision from Long-Term Filter Usage in Anomalous but Not Normal Trichromacy

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SUMMARY

For over 150 years, spectrally selective filters have been proposed to improve the vision of observers with color vision deficiencies [1]. About 6% of males and <1% of females have anomalies in their gene arrays coded on the X chromosome that result in significantly decreased spectral separation between their middle- (M-) and long- (L-) wave sensitive cone photoreceptors [2]. These shifts alter individuals’ color-matching and chromatic discrimination such that they are classified as anomalous trichromats [3, 4]. Broad-band spectrally selective filters proposed to improve the vision of color-deficient observers principally modify the illuminant and are largely ineffective in enhancing discrimination or perception because they do not sufficiently change the relative activity of M- and L-photoreceptors [5, 6]. Properly tailored notch filters, by contrast, might increase the difference of anomalous M- and L-cone signals. Here, we evaluated the effects of long-term usage of a commercial filter designed for this purpose on luminance and chromatic contrast response, estimated with a signal detection-based scaling method. We found that sustained use over two weeks was accompanied by increased chromatic contrast response in anomalous trichromats. Importantly, these improvements were observed when tested without the filters, thereby demonstrating an adaptive visual response. Normal observers and a placebo control showed no such changes in contrast response. These findings demonstrate a boosted chromatic response from exposure to enhanced chromatic contrasts in observers with reduced spectral discrimination. They invite the suggestion that modifications of photoreceptor signals activate a plastic post-receptoral substrate that could potentially be exploited for visual rehabilitation.

RESULTS AND DISCUSSION

The method of maximum likelihood difference scaling (MLDS) was used to obtain suprathreshold contrast scales that have the property that equal ordinate differences are perceptually equal [7, 8]. The method is based on a paired comparison of perceptual intervals. When three Gabor patterns (Equation 1) are presented as in Figure 1A, observers can readily indicate which of the two bottom patterns appears more similar to the standard above. Triplets chosen from 9 suprathreshold contrast levels spanning a 30-fold range were used to test contrasts that were varied in luminance or chromaticity (M- and L-cone modulation). When over repeated trials the observer chooses the left or right stimulus with equal frequency, we assume that the standard bisects the perceptual interval between the two lower stimuli. Based on a signal-detection model (Equations 2, 3, and 4), perceptual scales (parameterized as d’) were estimated for each of the 9 patterns by maximum likelihood that best predicted the observer’s choices over the full set of 84 ordered triplets. The resulting difference scale varies nonlinearly as a function of contrast and was fitted by nonlinear least-squares with a Michaelis-Menten function (Equation 4) so that the two parameters controlling the maximum response and rate of increase, Rm and ζ, respectively, could be estimated for each subject (example subject shown in Figure 1B). Figure 1C shows average curves obtained from 27 well-characterized participants (9 deuteranomalous, 9 protanomalous, and 9 normal trichromats) for contrasts modulated along each of two axes in color space [9]. The curves for luminance modulation (solid) are more similar for normal and anomalous trichromats than the curves for chromatic modulation (dashed), which show striking differences among the groups both in Rm (maximum contrast response or response gain) and ζ (contrast at which the response attains half of the maximal asymptotic response or inverse of contrast gain). Effective contrast reduction at the input due to the decreased spectral separation of the photopigments (Figure 1D) does not suffice to explain either the smaller Rm or smaller ζ of anomalous trichromats (Figure S1) [9].

Early-stage retinal processing involves a differencing operation between the M- and L-cone classes [13], illustrated by...
Figure 1. Experimental Design, Typical Results and Theoretical Analysis

(A) An ordered triplet of Gabor patterns varying in chromatic contrast from an MLDS trial. Observers fixated the cross and indicated which of the lower two stimuli was most similar to the standard on top. In separate sessions, the procedure was repeated using Gabor patterns varying in luminance contrast.

(B) Difference scale estimates from one normal trichromatic observer for luminance Gabor patterns. The results are means (±95% conf. int.) from 4 sessions, repeated on 2 separate days. The solid curve is the Michaelis-Menten model fit to the points by nonlinear least-squares; the parameters of the fit are shown by the inset.

(C) Average curves for normal (black), protanomalous (red), and deuteranomalous (green) trichromats. Solid curves denote response along a luminance (L+M) axis and dashed for chromatic (L–M) modulation (replotted from [9]) (also, see Figure S1). Contrast is specified, here and elsewhere in this article, as the nominal value with respect to the maximum attainable on the display.

(D) Spectral sensitivity of normal S, M, and L cones. M’ and L’ indicate sensitivity curves of anomalous observers (based on [4]). These estimates are for average observers, but polymorphisms result in individual differences in peak separation for both normal and anomalous trichromats [10–12].

(E) Difference spectra modeled for normal (L–M) and anomalous trichromats (Protan: M’–M; Deutan: L–L’) with weights adjusted for a null response from an equal-energy light.

(F) Optical density (-log10 transmission) plotted against wavelength for commercial filters designed to increase the differential stimulation of M and L cones. The dotted curve shows the spectral density of the control neutral density filter.

Figure 1E. Compared to normal trichromats, the reduced spectral separation on average attenuates the peak-to-trough signal to 41% and 25% of the normal, respectively, in protanomalous and deuteranomalous individuals. It might be expected that this signal loss would reduce perceived color differences along a post-receptoral L-M axis [14–16]. Evidence that the perceptual compression along an L-M axis is less than predicted has been proposed to be due to neural recalibration that generates compensatory post-receptoral gain amplification [9, 16–18], a hypothesis that is also supported by the steeper rise of the anomalous chromatic response curves in Figure 1C.

The proposition that by modifying the spectral distribution of light reaching the photoreceptors, color filters could affect chromatic discrimination and color perception, has had a long history. Maxwell [1] proposed the possibility of improving color discrimination with red and green filters placed over the eyes of a dichromat who entirely lacked M or L cones, but this approach has been shown to be of limited efficacy [19]. Even though such methods cannot lead to normal color vision, it might be thought that anomalous trichromacy would be more amenable to improvements with filtering by spectral reshaping of the three present classes of cone sensitivities. Broad-band filters may, indeed, help individuals with M- or L-cone deficiencies to defeat standard color vision tests by modifying the test illuminant. However, this does not imply that they improve color vision [5, 6]. In theory, a notch filter can achieve this.

We tested the long-term effects of wearing a commercial notch filter (EnChroma®), heretofore referred to as the test filter, on contrast response. The absorption spectra for indoor and outdoor versions of the filter are shown in Figure 1F. Participants (classified as described in STAR Methods) were male volunteers (8 anomalous and 2 normal trichromats) invited to wear glasses with either of the two notch filters shown. One of the anomalous trichromats was given a neutral density filter having approximately the same overall light attenuation as the indoor test filter. Observers kept a diary and reported estimated daily usage of the glasses (mean = 7.7 h/day, SD = 3.61). The participants mostly preferred the indoor version because they worked indoors and because some of the testing occurred during the worst wildfire in California history (known as the Camp Fire). Although it was about 100 km from the lab, the air was smoke filled, and the
sun was hidden for several weeks, minimizing the time spent outdoors.

Figure 2 presents MLDS results from one protanomalous observer evaluated without the test glasses on day 0 and on 3 subsequent tests after wearing the glasses. All tests were performed without the glasses. The top panels show the contrast responses estimated for chromatic (red points) and achromatic (black points) stimuli for each session. The solid curves are individually fitted Michaelis-Menten functions. To control for day-to-day variation in the estimated $R_m$ of the fitted functions, the chromatic (L-M) scale was normalized to the daily estimated $R_m$ of the achromatic scale (luminance), shown in the lower panels. Note that the ratio at the maximum contrast tested increased on day 2 and was above the day 0 baseline (dashed red line) on all subsequent days of testing.

Spontaneous comments followed the changes in objective testing. On day 2, this participant said, “I wear the glasses very often… I am certain that I am seeing differences in everything that has red in it (flowers, leaves, cars).” On day 4, he reported that “Autumn foliage colors are what is most noticeably changed.” On day 11, his relative chromatic response was lower than on day 4. Nevertheless, his relative chromatic response was still 72% above baseline. The small drop between days 4 and 11 may reflect his report that he only had worn the glasses once since the previous test date.

The pattern of results was consistent across subjects (Figure S2), although we did not identify differences between deuteranomalous and protanomalous observers (mean percentage change at day 11 for all subjects: 71%, 95% conf. int. = 45%–96%). Individual differences may reflect the amount of time observers wore the glasses as well as the recognized variability in anomalous cone spectral sensitivities [10, 11]. Six of the 7 anomalous observers who wore the test glasses made spontaneous comments indicating enhancement of the appearance of color with the glasses and when removed (Figure S2). Figure 3 shows average $R_m$ ratios (black circles) from all anomalous observers fitted with an exponential function (black curve). The results cannot be attributed to practice because the protanomalous observer wearing neutral density filters showed no changes over days and reported no changes in his color vision (Figure 3, green points, and Figure S3). As the neutral density filter reduced the overall intensity similarly to that of the test filter, the effect cannot be attributed to sensitization due to an average reduction in retinal illuminance.

The filters were designed to enhance chromatic contrasts for observers with anomalous cone photopigments. Analysis of their effects on chromatic contrast indicates that the filters effectively sharpen the 2 lobes of the L-M function and increase the separation of their peaks for both normal and anomalous observers. Normal observers sometimes report an effect of the filters on color appearance, but the two normal trichromats who wore the filters displayed no change in their chromatic contrast response relative to their achromatic contrast response (Figure 3, blue points, and Figure S3). Despite the small sample, the percentage change of the anomalous who wore the test glasses differs significantly from the combined normal and placebo groups (permutation test: n = 10,000, p = 0.008). The data of the normal observers provide a reference for evaluating the improvement observed for anomalous observers. From the fitted function (Equation 5), the $R_m$ of the average anomalous observer increased to 50% of its asymptotic value by 5.9 days.

For all anomalous subjects, there was no statistically significant change in response gain along the luminance axis (likelihood ratio test: $\chi^2(1) = 3.38, p = 0.07$). Along the L-M axis, anomalous observers showed a negative linear trend in the log contrast gain over days ($\chi^2(1) = 4.58, p = 0.03$), but the slope indicated that the change per day was quite modest (0.021, 95% confidence interval (–0.040, –0.002)). Over 11 days, this
in the world [18, 20] have received some empirical support [17, 19, 21]. While we recently reported higher chromatic contrast gain in anomalous observers [3], the results here demonstrate that the mechanism controlling chromatic response gain also displays plasticity when exposed to an enhanced chromatic environment. Thus, the current results align more closely with changes in luminance contrast discrimination obtained from long-term filtering of contrast [22] that could be described solely by a change in response gain. While the sensitivity improvements reported in this previous study resulted from extended exposure to contrast reduction, paradoxically, the increased response gain reported here is found subsequent to long-term exposure to contrast enhancement. This apparent contradiction suggests an alternate explanation based on a perceptual learning mechanism. In spite of evidence supporting gain amplification at low contrasts, anomalous trichromats display a lower maximum response to chromatic contrast [9], indicating an attenuated chromatic response system. The contrast response enhancements generated by the filters may have led the observers to become more aware of weak perceptual signals and, thus, to have learned to be more attentive to them. Under this hypothesis, the increased chromatic response gain might persist indefinitely. Indeed, intensive behavioral training methods have been reported to improve vision in amblyopia and stereoblindness via perceptual learning mechanisms [23, 24]. In the current study, however, the increases in contrast response remarkably resulted from only passive usage of the filters.

More than 160 years ago, James Clerk Maxwell tested whether red and green lenses could help a dichromat discriminate colors by binocular color mixtures. He was hoping that “the mental processes may become so familiar … as to act unconsciously like a new sense,” ([1], p. 287) causing lasting improvement in color vision. This study tested anomalous trichromats who may indeed experience sustained improvements in their color vision. In this regard, the comment of a deuteranomalous observer is telling when he reported, “I now see that my girlfriend’s brown hair has hints of red…; I now notice it even without wearing the glasses.”

**STAR METHODS**

Detailed methods are provided in the online version of this paper and include the following:

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**SUPPLEMENTAL INFORMATION**

Supplemental information can be found online at https://doi.org/10.1016/j.cub.2020.05.054.
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AUTHOR CONTRIBUTIONS

Conceptualization, J.S.W. and K.K.; Methodology, J.S.W. and K.K.; Software, K.K and B.M.A.; Investigation, B.M.A.; Formal Analysis, J.S.W., K.K., and B.M.A.; Writing – Original Draft, J.S.W.; Writing – Review & Editing, J.S.W., K.K., and B.M.A.

DECLARATION OF INTERESTS

KK holds shares in EnChroma®. The authors declare no competing interests.

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STAR METHODS

KEY RESOURCES TABLE

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|---------------------|--------|------------|
| Deposited Data      |        |            |
| Source data for figures | This study | https://datadryad.org/stash/share/UhBmhp_o_kEAg6r7Qk-jrx1rCEM0vY3cLGmyUp3qKQ8 |
| Software and Algorithms |        |            |
| PsychoPy3            | [25]   | https://www.psychopy.org |
| R                   | [26]   | https://www.r-project.org |
| MLDS                | [8]    | https://CRAN.R-project.org/package=MLDS |
| nlmee               | [27]   | https://CRAN.R-project.org/package=nlmee |
| Cambridge Color Test | [28]   | https://www.crsfid.com |
| Other               |        |            |
| EnChroma® glasses   | N/A    | https://enchroma.com |
| Neitz OT anomaloscope | [29]   | http://neitz-ophthalmic.com/products/ophthalmic/anomalo/ot.html |
| Eizo FlexScan T566  | N/A    | https://www.eizoglobal.com/ |
| Farnsworth F2 Plate | Medical Res. Laboratory US Navy, New London, CT | N/A |
| Farnsworth Panel D-15 | [29] | https://www.pantone.com |
| Hardy-Rand-Rittler pseudoisochromatic | [30] | https://premierop.com |
| Verilux Illuminant C lamp | [29]  | https://www.good-lite.com/Details.cfm?ProdID=720 |
| 2-button Bluetooth response pad | Custom Modification | https://www.dell.com |
| SpectraScan Spectroradiometer 670 | N/A | https://www.photoresearch.com/content/quicktab-spectroradiometers-670-system-options |

RESOURCE AVAILABILITY

Lead Contact
Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, John S. Werner (jswerner@ucdavis.edu). There is no restriction for distribution of materials.

Materials Availability
This study did not generate any new reagents.

Data and Code Availability
Experimental methods used PsychoPy3. Curve fitting and statistical analyses used R. Source data for the figures in this paper are archived at https://datadryad.org/stash/share/UhBmhp_o_kEAg6r7Qk-jrx1rCEM0vY3cLGmyUp3qKQ8

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Ten volunteers participated in this study. They were recruited through flyers and an online portal. Written informed consent was obtained using a protocol approved by the University of California, Davis, Institutional Review Board. Subjects were compensated for their participation.

All observers had normal visual acuity (best corrected to 6/6 or better) and had a negative history of retinal disease and neurological disorders affecting vision. Male observers (18-36 years of age) from our previous study [9] were invited to participate in this experiment to evaluate whether color vision was affected by wearing spectral notch filters (EnChroma®). Among these observers, 5 deuteranomalous and 3 protanomalous individuals volunteered to wear the glasses. One of the protanomalous observers wore neutral density filters that had the same average absorbance as the notch-filtered glasses. There were also two normal trichromats who wore the test glasses. Participants were not informed of the glass manufacturer or whether they were provided neutral density filters.
Observers were tested (day 0) and subsequently provided glasses. They were asked to wear them as much as possible. They were then re-tested on days 2, 4 and 11. All testing was performed without the glasses. Spontaneous comments during rest periods and before or after testing were recorded.

Color vision classification was based on Rayleigh matches with a Neitz OT anomaloscope and the Cambridge Color Test (CCT) administered in trivector mode using a calibrated monitor (Eizo FlexScan T566). Observers with anomaloscope coefficients between 0.766 and 1.333 were classified as normal. Deuteranomalous observers were identified as those individuals with values above this range and protanomalous below. On the CCT, the two participants classified as normal had deutans and protan vector lengths < 100 with mean values of 47 and 65, respectively. For subjects classified as deuteranomalous, the deutans and protan vector means were 551 and 293, respectively. For subjects classified as protanomalous, the deutans and protan vector means were 272 and 676, respectively. This comports with the criteria for classification of normal and anomalous for the CCT. Additional confirmation of classifications was based on the F2 Plate test, the Farnsworth Panel D-15 test, and the American Optical Hardy-Rand-Rittler pseudoisochromatic plates, all administered under a lamp equivalent to illuminant C.

**METHOD DETAILS**

All experiments were performed using an Eizo (FlexScan T566) CRT monitor with a 40.3 cm diagonal screen size operating at a resolution of 1280 × 1024 pixels viewed at a distance of 150 cm. The visual path from viewer to stimuli was surrounded by black light baffles internally coated by non-reflective fabric. Observers were refracted for the test distance using standard trial lenses rather than their habitual spectacles if they were tinted or had anti-reflective coating.

Stimuli were displayed with 10-bit color resolution using custom code written in Python 2.7 utilizing the PsychoPy3 package and integrated development environment [25]. Responses were recorded with a 2-button Bluetooth response pad (Dell). The display monitor was gamma corrected and chromatically calibrated using a SpectraScan Spectroradiometer 670 placed 150 cm from the screen and the PsychoPy3 IDE’s Monitor Center automated screen calibration tool.

Each stimulus was a horizontal Gabor pattern (1 c/deg carrier and standard deviation, 4 deg diameter envelope) defined by

\[ f(x, y) = L_2 \left( 1 + c_t \exp \left( -\frac{x^2 + y^2}{2} \right) \sin 2\pi y \right) \]  

(Equation 1)

where \( L_2 \) is the mean luminance of the screen, \( x, y \) position in degrees, and \( c_t \) the contrast of the carrier signal along the axis \( \theta \) in color space. The sign of the Gabor term was chosen randomly across trials to generate stimuli varying in phase by 180 deg in order to minimize local adaptation and afterimages. Contrast was specified in nominal machine units, i.e., with respect to the maximum contrast obtainable on the display.

The stimuli were truncated at 4 deg diameter (4σ) and were in sine phase so that both the space-average luminance and chromaticity did not vary. The patterns were offset from a fixation cross. Modulation of Gabor patterns was along a luminance axis ([90,0,1], [elevation, azimuth, maximum contrast] in the Derrington-Krauskopf-Lennie (DKL) color space or an L-M axis in the isoluminant plane ([0,0,1] in DKL color space) [31]. A brief warning tone preceded each stimulus presentation of 500 ms duration. The steady background was achromatic (Commission Internationale de l’Eclairage (CIE) \((x, y) = (0.33,0.35); Y = 48.1 \text{ cd/m}^2\)) and continuously present. Contrasts in all graphs are specified as nominal or machine unit contrasts, i.e., with respect to the maximum contrast obtainable on the display. Using the DeMarco, Pokorny and Smith [4] cone spectral sensitivities for average observers with each color vision type, the maximum L-M cone contrasts that could be displayed were estimated as: Normal 0.142, Protanomalous 0.037, and Deuteranomalous 0.041. The CIE \((x, y)\) coordinates of these extreme values along the L-M axis were calculated as (0.310, 0.484) and (0.342, 0.226) for protanomalous and deuteranomalous observers, respectively.

Maximum Likelihood Difference Scaling (MLDS) was used to estimate suprathreshold contrast response [9]. In the experimental task, each trial consisted of the presentation of ordered triplets (randomly chosen as descending or ascending) that were modulated in luminance (achromatic condition) or along an axis that stimulated M- and L-cones (chromatic condition) at constant luminance in DKL space on a CRT monitor. Testing of chromatic and achromatic stimuli was performed in separate runs. Nine contrast levels were tested, evenly spaced on a log contrast scale, with the lowest chosen to be clearly detectable, low contrast, denoted by \( c_0 \), estimated in a preliminary experiment as 1.7 times a threshold value determined by a Yes/No procedure and the highest at 90% of the maximum nominal display contrast. This resulted in a set of stimuli that were easily ordered in contrast by the subjects. On each trial, three randomly chosen contrast levels were presented for 500 msec; the mid-level contrast stimulus served as a standard, and the higher and lower contrast stimuli were presented below, randomly to the left or right (Figure 1A). The task was to indicate, by a button press, which stimulus displayed below was most similar to the standard.

**QUANTIFICATION AND STATISTICAL ANALYSIS**

**Fitting Maximum Likelihood Difference Scales**

The logic and observer model for MLDS is as follows. Given a set of \( p \) stimuli ordered along a physical continuum, triples or non-overlapping quadruples are sampled on each trial. Here, we used the method of triads, so we will develop the model in terms of triples.
Given a trial with the triple of physical contrasts \( \phi(a) < \phi(b) < \phi(c) \), we assume a mapping (not necessarily monotonic) onto internal responses, \( \psi(a), \psi(b), \psi(c) \). The observer considers the noise-perrupted internal decision variable

\[
\delta(a, b, c) = (\psi(b) - \psi(a)) - (\psi(c) - \psi(b)) + \epsilon = 2\psi(b) - \psi(a) - \psi(c) + \epsilon = \Delta(a, b, c) + \epsilon,
\]

(Equation 2)

where we have abbreviated \( \phi(a) \) by \( a \), etc. and \( \epsilon \sim N(0, \sigma^2) \). The random perturbation, \( \epsilon \), is called the judgment noise and provides for inconsistencies in the observer’s responses when \( \Delta(a, b, c) \) is sufficiently small. If on a given trial \( \delta < 0 \), the observer chooses \( a \), otherwise \( c \). We code the observer’s responses, \( R_i \), by 1 or 0 depending on whether the choice is stimulus \( a \) or \( c \). From the ensemble of responses to all triads, we compute the log likelihood function for a Bernoulli distributed variable

\[
\ell(\Psi : R) = \sum_{i=1}^{n} R_i \log \left( \frac{\Phi \left( \frac{\Delta}{2\sigma} \right)}{1 - \Phi \left( \frac{\Delta}{2\sigma} \right)} \right) + (1 - R_i) \log \left( 1 - \Phi \left( \frac{\Delta}{2\sigma} \right) \right).
\]

(Equation 3)

where \( \Phi \) is the cumulative distribution function for the standard Gaussian, \( R \) is the vector of responses to all triads and \( \Psi \) is the vector of scale values, \( \psi_i \). The scale values and judgment noise are chosen as the values that maximize Equation 3. While it appears that the model requires estimation of \( r + 1 \) parameters, to obtain an identifiable solution, we fix the lowest value at 0 and \( \psi_0 \) is the asymptotic maximum response, taken as a measure of response gain, and \( \zeta \) the semi-saturation constant, which is reciprocally related to the contrast gain. The effect of the term \( \psi_0 \) is to translate the function along the contrast axis. Thus, the value of \( \zeta \) is specified with respect to the value of \( \psi_0 \). Elsewhere, we argued that a better measure of gain is provided by the ratio of contrasts \( c_0/(c_0 + \zeta) \), which is invariant on a logarithmically scaled abscissa. The asymptotic value given by the value of \( R_m \) is indicated by the dashed gray line in Figure 1B. Except for Figure S1, we use a linear contrast axis throughout this article to emphasize the value of \( R_m \).

For anomalous observers, the changes in maximal response, \( R_m \), due to long term usage of the test glasses were analyzed with a nonlinear mixed-effects model [26] with the variation across days, \( d \), described by an exponential model,

\[
G_0(d) = R_0 + (k + K_0) \left( 1 - \exp \left( \frac{d}{\tau + t_0} \right) \right) + \epsilon_i,
\]

(Equation 5)

where \( G_0 \) is the maximal response of observer \( o \), \( R_0 \) is the normalized value of \( R_m \), at day 0, prior to wearing the glasses, \( k \) and \( \tau \) are estimated fixed-effect parameters indicating the amplitude of change and the exponential time constant, respectively. The residuals, \( \epsilon_i \), are assumed to be Gaussian distributed with mean 0 and variance \( \sigma^2 \). In addition, observer-dependent random effects, \( K_0 \) and \( t_0 \) for the two fixed-effects estimated parameters were assumed to be Gaussian distributed with mean 0 and variances \( \sigma_{K_0}^2 \) and \( \sigma_{t_0}^2 \), respectively. In the course, of fitting the model, the random effect of the time constant was found not to improve the fit significantly and was subsequently dropped from the model.

For the normal observers and the placebo observer, long-term usage was assessed with a linear model,

\[
G(d) = \beta_0 + \beta_1 d + \epsilon_i,
\]

(Equation 6)

where \( \beta_0 \) and \( \beta_1 \) are the slope and intercept, respectively, and the hypothesis that the slope differed from 0 was tested with a t-statistic.
Permutation tests were performed by a custom written script in R [26] available upon request. In short, the maximum percentage change for each observer was assigned to a test or control group. The assignment of the labels was permuted 10000 times and the difference of the means of the two groups computed for each permutation. The two-tailed p value was computed as the number of times the absolute value of the permutation differences was greater than or equal to the absolute value of the observed difference divided by 10001.