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Retina

Transcorneal Electrical Stimulation Dose-Dependently Slows the Visual Field Loss in Retinitis Pigmentosa

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Purpose: To assess whether transcorneal electrical stimulation (TcES) current-dependently slows progressive loss of visual field area (VFA) in retinitis pigmentosa (RP).

Methods: Data from 51 patients with RP who received monocular TcES treatment once weekly over 1 year in an interventional, randomized study have been analyzed a posteriori. Current amplitudes were 0.1 to 1.0 mA in the TcES-treated group ($n = 31$) and 0.0 mA in the sham group ($n = 20$). VFA was assessed in both eyes (semiautomatic kinetic perimetry, Goldmann targets V4e, III4e). Annual decline rate (ADR) of exponential loss and model-independent percentage reduction of VFA at treatment cessation were correlated to current amplitude.

Results: For V4e, mean ADR was −4.1% in TcES-treated eyes, −6.4% in untreated fellow eyes, and −7.2% in placebo-treated eyes; mean VFA reduction in TcES-treated eyes was 64% less than in untreated fellow eyes ($P = 0.013$) and 72% less than in placebo-treated eyes ($P = 0.103$). Individual VFA reductions correlated with current amplitude ($P = 0.043$) and tended toward zero in patients who received 0.8 to 1.0 mA. For III4e, there was a marginally significant current-dependency of interocular difference in reduction ($P = 0.11$). ADR and VFA reduction did not significantly correlate with baseline VFA.

Conclusions: Loss of VFA (V4e) in patients with RP was significantly reduced in treated eyes compared to untreated eyes by regular use of TcES in a dose-dependent manner. No dependence of effects on the initial extent of VFA loss was found.

Translational Relevance: TcES provides potential for preservation of visual field in patients with RP.

Introduction

Retinitis pigmentosa (RP) comprises a group of inherited retinal diseases associated with progressive visual loss.[1] It seriously impacts the quality of life of patients with RP.[2] Typically, RP begins with a degeneration of rods in the peripheral retina followed by a loss of cones. The visual field area (VFA) and the corresponding retinal area decrease exponentially over time,[3,4] with an annual decline rate (ADR) between 5% and 17%, depending on the genetic cause, measurement of VFA, and definition of ADR.[3–7]

To preserve or restore vision in RP, gene replacement therapies,[8] stem cell therapies,[9] optogenetic therapies,[10] and electronic implants[11] are under development. However, with few exceptions, such as gene therapy for RPE65-associated retinal dystrophy,[12] no such method is yet available for routine clinical use.[13,14] A physical treatment approach is transcorneal electrical stimulation (TcES), which has been described as a promising strategy for RP.[15–19] TcES has a manifold body of evidence from large clinical trials and is available as therapy in Europe.[20–24] It aims to activate neuroprotective factors and pathways in the retina and retinal pigment epithelium to enhance survival or regeneration of photoreceptors and thereby halt or, at

least, slow disease progression. In mathematical terms, TcES intends to increase the time constant of the exponential progression or, equivalently, to decrease the ADR.

The mechanism of action of TcES has not yet been fully understood. Preclinical studies have shown that electrical stimulation activates antiapoptotic and neuroprotective pathways and suppresses inflammatory signaling pathways, thereby producing a cell-preserving effect in the retina (see reviews[15–17]). The cellular and subcellular effects in the retina elicited by electrostimulation depend on the stimulus intensity.[25–29] Clinical studies showed that TcES caused a significant increase in blood flow to the central retina,[30,31] increased oxygen consumption by retinal cells,[23] improved visual acuity,[22,30,32] slowed visual field loss[21] or improved visual field,[30,33] improved b-wave amplitudes, and shortened electroretinography latencies.[21,22,33] For a comprehensive summary of clinical studies of TcES in RP, see Liu et al.[24]

In most clinical studies, stimulation intensity for TcES has so far been determined based on multiples of the individual electrical phosphene threshold (EPT, the current strength at which perception of light is elicited[34]). To date, however, no dose–response curves have been evaluated that establish a relationship between the intensity of TcES and clinically relevant determinants such as visual field. We conducted an a posteriori analysis of VFA data of an earlier clinical study (EST2 trial[21]) to explore the hypothesis that TcES can slow the progression of the decline in VFA in RP and that the treatment effect depends on the current strength. Additionally, we investigated whether the TcES effect depends on the VFA at baseline and whether TcES shows a current-dependent effect on safety parameters.

Methods

Patient Selection and Study Design

We performed an a posteriori analysis of data from 52 adult patients with RP who had participated from 2011 to 2014 in the interventional, randomized EST2 trial (clinicaltrials.gov NCT01837901) at the University Eye Hospital Tübingen and completed the study according to protocol. The protocol was approved by the ethics committee of the Medical Faculty of the University of Tübingen. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki of 1975, as revised in 2008. Informed consent, including the long-term retention of data for future reanalyses, was obtained from all patients prior to inclusion into the study. The study was conducted according to the standards of good clinical practice, the European Union Directive for Medical Devices, and the German Medical Device Act.

Patients were examined at 14 visits over a period of 78 weeks: one screening visit, followed by 12 visits in weeks 1, 2, 3, 4, 10, 16, 22, 28, 34, 40, 46, and 52 and one follow-up visit in week 78 (dates deviated by a maximum of ±1 week). Visual field measurements were performed at screening and in weeks 1, 16, 28, 40, 52, and 78.

All patients had advanced rod-cone dystrophy. Mean age was 46 ± 15 years. Inclusion criteria included visual acuity (VA) 1.7 to 0.05 (logarithm of the minimum angle of resolution) and VFA >150 deg^2. For further inclusion and exclusion criteria and details of patient population, study protocol, and methods, see the original publication.[21]

Stimulation and Visual Field Examination

Patients were randomly assigned to treatment with 0.0 mA (placebo), 150% or 200% of their individual EPT (Fig. 1, Table 1). Treatment was performed monocularly, and the fellow eye received identical EPT tests, electrode contacts, and measurements but treatment with zero current. The DTL-type OkuEl thread electrode (Okuvision GmbH, Reutlingen, Germany) was positioned on the lower eyelid and contacted the ocular surface on the inferior limbus. The worse eye, determined at screening, was selected as the treated eye. Primary criterion was VA, and secondary criterion was VFA. In cases where both eyes were equally good, the patients could choose. In patients who had already been monocularly stimulated in a previous study, the unstimulated eye was selected for treatment.

TcES treatment was applied from weeks 1 to 52, once per week for 30 minutes, with biphasic current pulses (safety limit 1.6 mA, 5 ms each phase, 20 Hz; OkuStim system, Okuvision GmbH, Reutlingen, Germany). All patients conducted the stimulation at home. At each visit, EPTs were newly determined, and current amplitudes were readjusted accordingly (Figs. 2A, B).

The primary outcome parameter was VFA, as measured with an Octopus 900 perimeter (Haag-Streit, Inc., Koeniz, Switzerland). For semiautomatic kinetic perimetry up to 90° eccentricity, white stimuli (Goldmann targets III4e and V4e with a constant angular velocity of 3°/s) were used. Isopter and scotoma areas (in deg^2) were quantified using the built-in software algorithm.

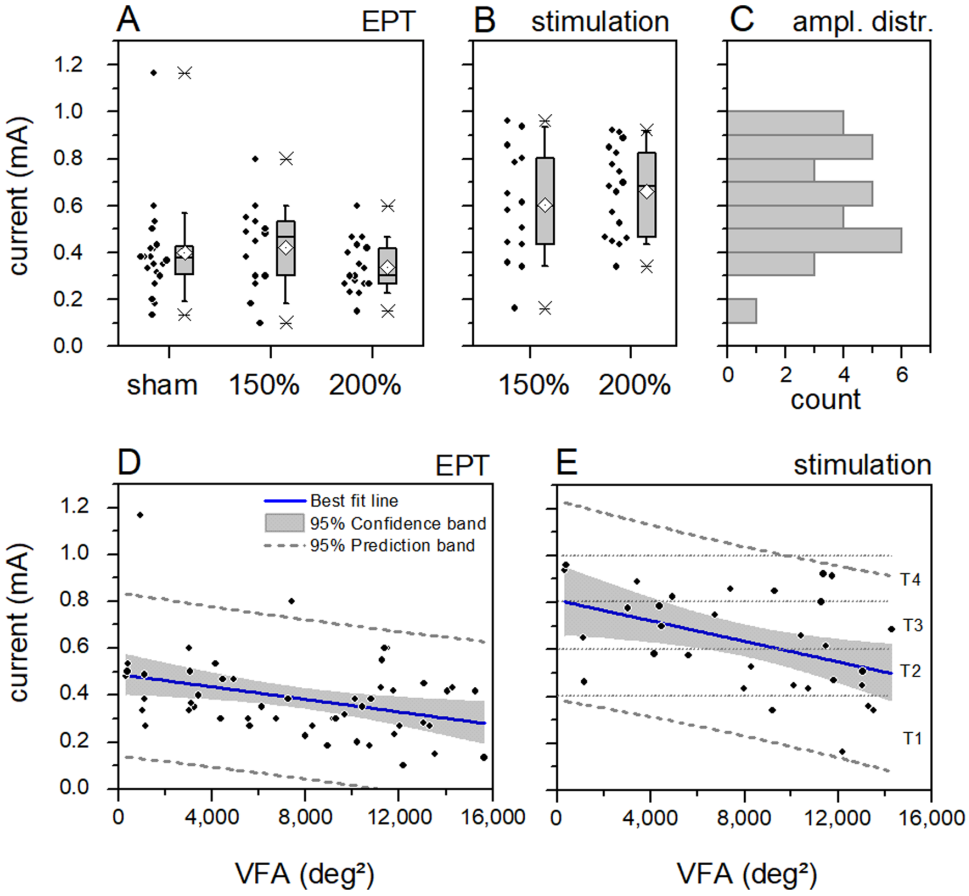

Figure 1. EPTs and amplitude of stimulation current derived therefrom. (A) Distribution of the EPT of the treated eyes in the sham group and in the groups 150% and 200% EPT at visit 1. The *lower* and *upper whiskers* of the boxes represent the 10th and 90th percentiles, and the *lower* and *upper borders* of the boxes represent the first and third quartiles. The *horizontal bar* within the boxes represents the median, the *white square* the mean. (B) Distribution of the mean current amplitudes applied to patients in the 150% and 200% EPT groups. (C) Histogram of the distribution of the current amplitudes of the merged 150% and 200% EPT groups. (D) Correlation between EPT and VFA (target V4e) of the treated eyes at visit 1. *Blue line*: linear fit curve; *gray area*: 95% confidence band for regression line. *Dashed gray lines*: 95% prediction band. r^2: 0.122, $P = 0.012$. (E) Correlation between mean amplitudes of the stimulation current and VFA (V4e) of the TcES-treated eyes at baseline. r^2: 0.198, $P = 0.012$. *Horizontal dashed lines* mark the ordinal current ranges defined in Table 2.

Data Analysis

We analyzed data from treated eyes and as intraindividual, interocular control from untreated fellow eyes. In one patient, the visual field in both eyes decreased by 80% in less than 10 months during the study. Due to this exceptionally rapid decrease, data of this patient were excluded from further analysis. To correlate the

Table 1. Definition of Groups in Original Analysis (Study Groups) and for A Posteriori Analysis

		Groups		
Eyes	Treatment	Study Groups	A Posteriori Analysis	
Treated eyes	TcES	150% EPT	T	T1 $n = 4$
		$n = 15$	$n = 31$[a]	T2 $n = 10$
		200% EPT		T3 $n = 8$
		$n = 17$		T4 $n = 9$
	Placebo		sham $n = 20$	
Untreated fellow eyes[b]		$n = 52$	$n = 51$[a]	

T1–T4 are subgroups of treated group T with increasing current ranges (see Table 2).
[a]Due to an exceptionally rapid decrease of VFA, one patient was excluded from further analysis.
[b]In each group, the number *n* of treated and untreated fellow eyes is identical.

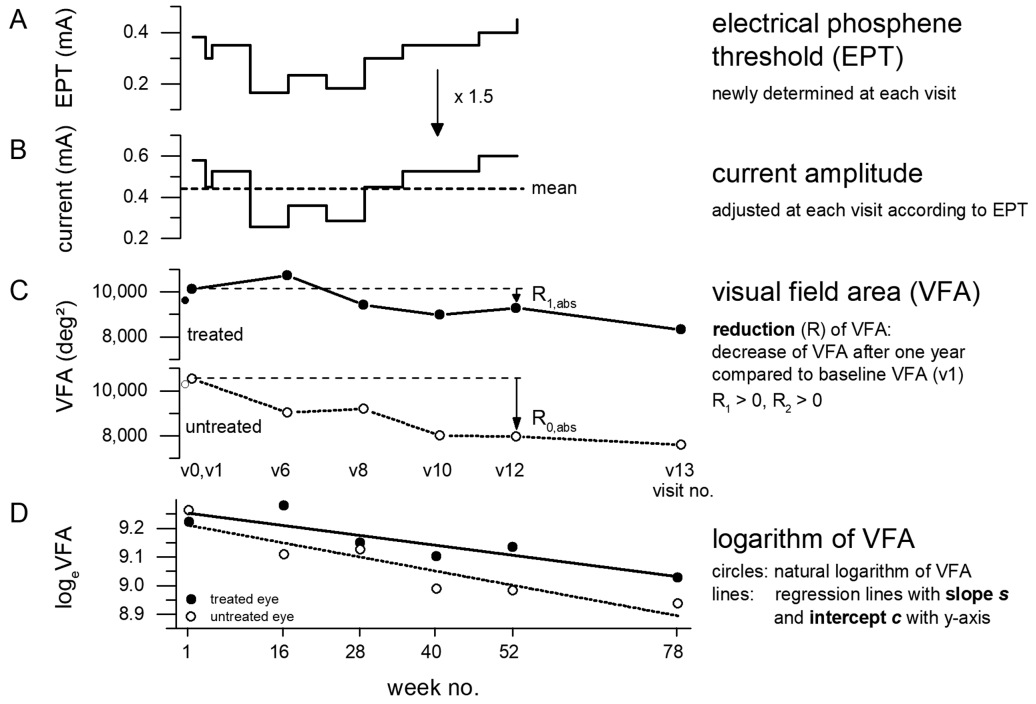

Figure 2. Example of one individual time course of stimulation and VFA (Goldmann target V4e) from a patient in the 150% EPT group. (A) EPT from visits 1 to 12. (B) Amplitude of the stimulation current (150% EPT, *solid line*) and mean current amplitude (*dashed line*). Stimulation started at visit 1 in week 1 and ended at visit 12 in week 52. At each visit, the EPT was determined and the current amplitude adapted accordingly. (C) Courses of the VFAs of the treated and untreated eyes from weeks 1 to 78 and definition of VFA reduction. VFAs were measured at screening (*small circles* at visit 0) and in weeks 1, 16, 28, 40, 52, and 78. (D) Natural logarithm of VFA (*circles*) and best-fit lines from linear regression over time from visits 1 to 78.

effects of TcES with stimulation intensity, the average current amplitude during the 12-month treatment was calculated for each patient (Fig. 2B).

To examine the influence of TcES treatment on the VFA time course and to determine the mean ADR of a patient group, the values of the VFA courses were normalized for each eye separately by dividing by the value from visit 1 (see overlay of VFA% time courses in Figures 3A1–F1 [V4e] and Supplementary Fig. S4 [III4e]). Assuming an exponential course over time, the VFA% values were averaged at each visit within the group and the mean VFA% transformed into the natural logarithm ($\log_e$VFA%). The $\log_e$VFA% values of the visits in the treatment period from weeks 1 to 52 were plotted as a function of time (Figs. 3A2–F2 [V4e] and Supplementary Fig. S4 [III4e]) and subjected to a linear regression analysis with the intercept fixed to zero. To investigate aftereffects of TcES treatment after discontinuation of stimulation, data from the follow-up visit in week 78 were included in a second linear regression of the $\log_e$VFA% values. The slope s (unit: 1/y) of the best-fit line was used to calculate the ADR of the group according to Equation (1). A negative ADR means a decrease of the VFA over time, and a positive ADR represents an increase.

$$ADR = e^{1y*s} - 1 \quad (1)$$

To determine the current dependence of the decline, VFA values were transformed into the natural logarithm ($\log_e$VFA) and subjected to a linear regression (Fig. 2D) from weeks 1 to 52 and additionally from weeks 1 to 78. A selection of $\log_e$VFA courses is presented in Supplementary Figure S1. The slopes s of the best-fit lines and interocular differences Δs in the slopes of the individual $\log_e$VFA courses of the treated and untreated eyes were correlated to the mean current amplitudes (Fig. 4). As the slope has a negative sign if VFA decreases over time, a positive Δs means a slower decrease in the VFA of the treated eye than in the untreated eye.

If electrical stimulation influences the time course of degeneration, the progression of visual field loss may deviate from a simple exponentially decreasing course. Therefore, as a model-independent measure of the effect of TcES, we determined the individual reductions $R_{1,abs}$ and $R_{0,abs}$ of the VFA from baseline to week 52 in the treated and untreated eyes

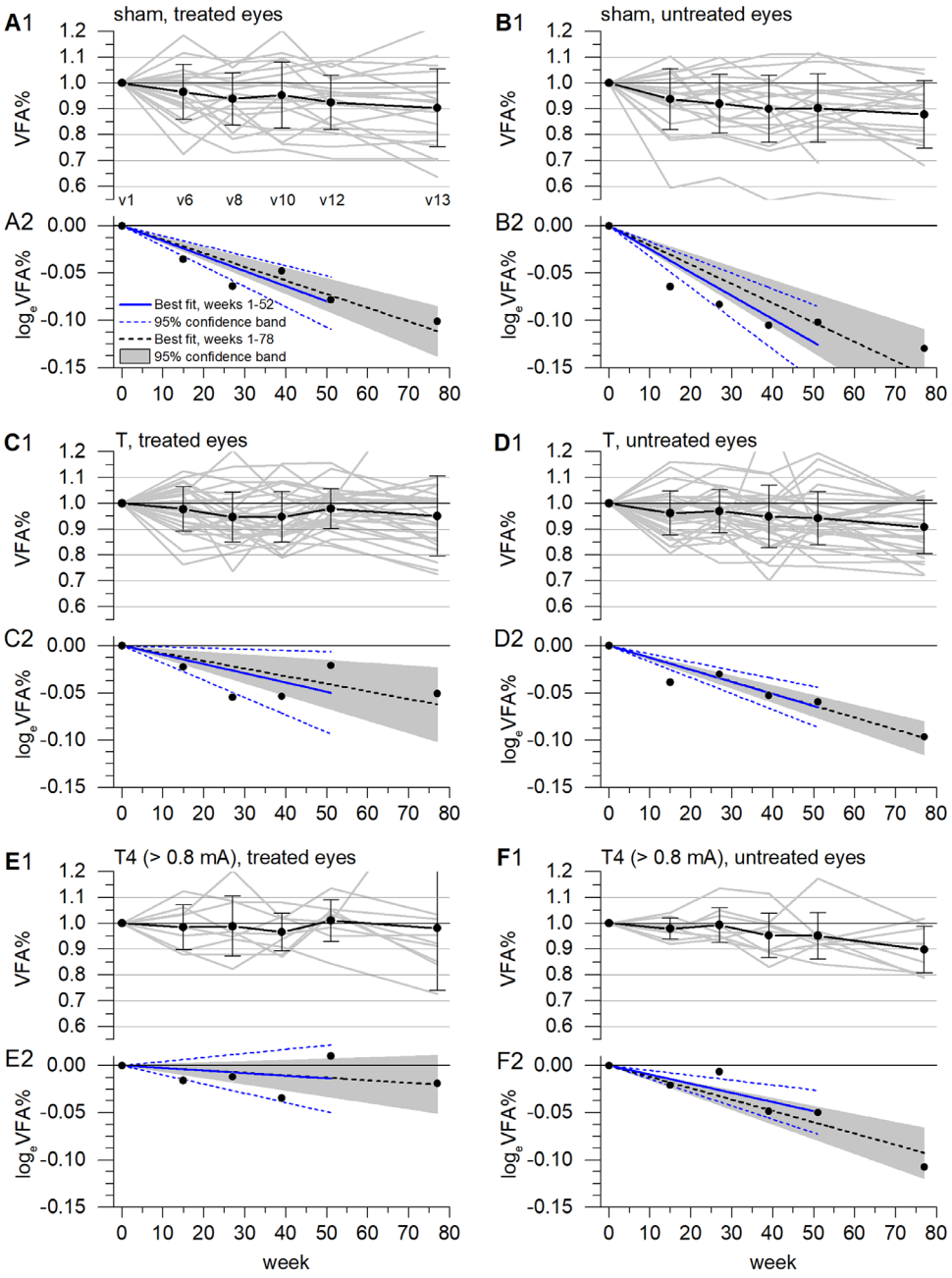

Figure 3. Normalized (VFA%) and logarithmized (log$_e$VFA%) time courses of VFA for Goldmann target V4e. (A) Sham group, treated eyes. (B) Sham group, untreated eyes. (C) Treated group T, treated eyes. (D) Treated group T, untreated eyes. (E) Subgroup T4, treated eyes. (F) Subgroup T4, untreated eyes. (A1–F1) Overlay of VFA% courses of all patients (*gray lines*) and the averaged course of the group (*circles* and *black line*). Time courses have been normalized to the VFA value at visit 1. *Black circles* depict the mean of the values of all patients in the group at a given visit, and *error bars* represent the SD. (A2–F2) Logarithm (*circles*) of the group means of VFA% values at each visit. *Solid* and *dashed blue lines* present the linear regression from weeks 1 to 52 and the 95% confidence band for the regression line; *dashed black lines* present the linear regression from weeks 1 to 78, and the *gray area* indicates the 95% confidence band for the regression line. Fitting has been performed with the intercept of the regression line fixed to zero. For slopes of regression lines, see Table 3.

for each patient (Fig. 2C) and the percentage reductions R_1 and R_0 by dividing $R_{1,abs}$ and $R_{0,abs}$ by the respective VFA value at visit 1 (baseline). We then analyzed the dependence of R_1 and R_0 and the interocular difference $\Delta R = R_1 - R_0$ on the individual mean current amplitudes (V4e: Figs. 5D–F, III4e: Supplementary Figs. S5D–F). As R_1 and R_0 have a positive sign if VFA decreases over time, a negative ΔR indicates less loss of VFA in the treated eye than in the untreated eye after 1 year. With an ideal exponential

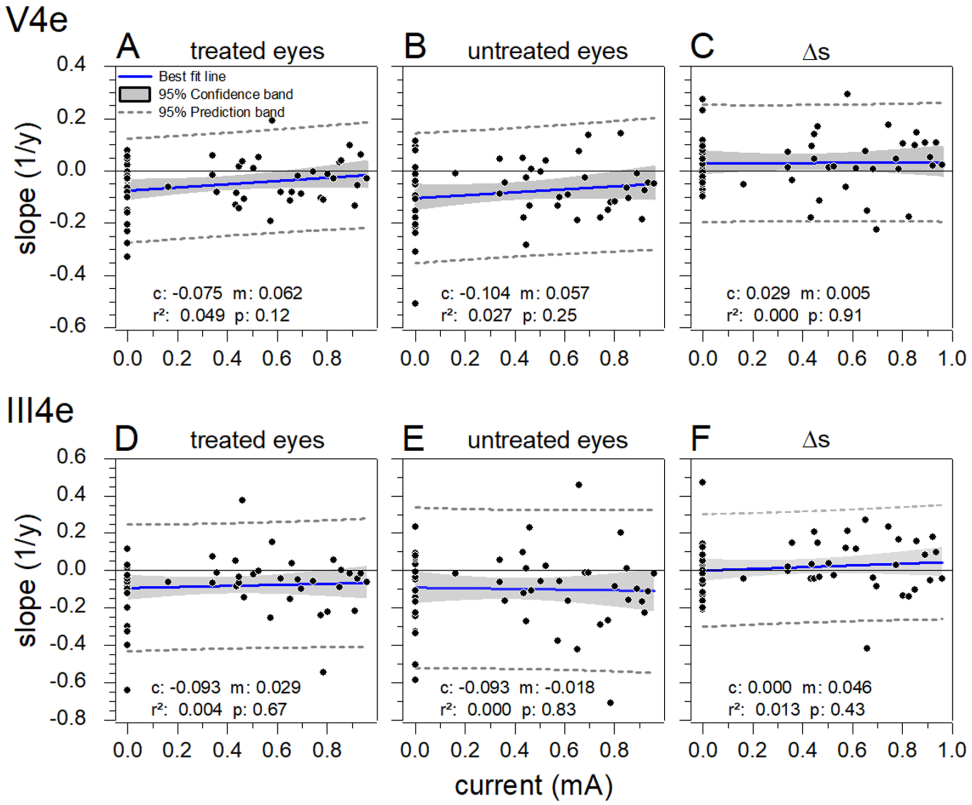

Figure 4. Current strength-dependence of slopes of the regression lines (weeks 1 to 52) of the individual $\log_e$VFA time courses in treated and untreated eyes as a function of the current amplitude for Goldmann targets V4e (A–C) and III4e (D–F). (A, D) Slopes of all treated eyes. (B, E) Slopes of all untreated eyes. (C, E) Individual interocular difference Δs of the slopes of the treated and untreated eyes. All data points have been included in the regression analysis (*blue line*: best fit), including those from the sham group (*dots* at 0.0 mA). *Gray areas* depict the 95% confidence bands for the regression lines, and *gray dashed lines* represent the 95% prediction bands. c is the intercept, and m is the slope of best-fit line.

course of the VFA progression, percentage reduction multiplied by –1 would correspond to the ADR. We further analyzed a possible linear dependence of the ADR and the reductions R on the initial VFA (Fig. 6 [V4e], Supplementary Fig. S6 [III4e]).

Statistical Analysis

Patients in the original study groups (150% EPT, 200% EPT) were pooled into a single TcES-treated group (group T) and compared with the placebo-treated group (sham group, Table 1). To analyze model-independently a possible dependence of treatment effects on current strength, these patients were further divided according to the individual stimulus intensity into four subgroups (T1–T4) with ordinal current ranges with cut-points 0+, 0.4, 0.6, and 0.8 mA (Table 2B).

To calculate intervisit correlation and test–retest variability, the VFA values obtained from visit 0 (screening) and visit 1 (baseline) were correlated to each other (Supplementary Figs. S2A, D) and compared according to Bland and Altman[35] (Supplementary Figs. S2B, E). The percentage test–retest variability (TRV) was calculated for each eye using Equation (2)[36]:

$$TRV = \frac{abs\left(VFA\left(visit\ 0\right) - VFA\left(visit\ 1\right)\right)}{\left(VFA\left(visit\ 0\right) + VFA\left(visit\ 1\right)\right)/2} \times 100 \quad (2)$$

We defined the 95% coefficient of repeatability ($CR_{.95}$) as the 95th percentile of the distribution of the individual TRV values (Supplementary Figs. S2C, F). These measures have also been used to characterize the interocular variability between the treated and untreated eyes (Supplementary Fig. S3).

For testing the equality of the EPT medians in the study groups (sham, 150% and 200% EPT), we used the Kruskal–Wallis test. Tests of an effect of TcES treatment on interocular differences in reductions R_1 and R_0 were performed using the paired Wilcoxon signed rank test. Tests of a difference between groups of unequal size and unpaired samples (treated group

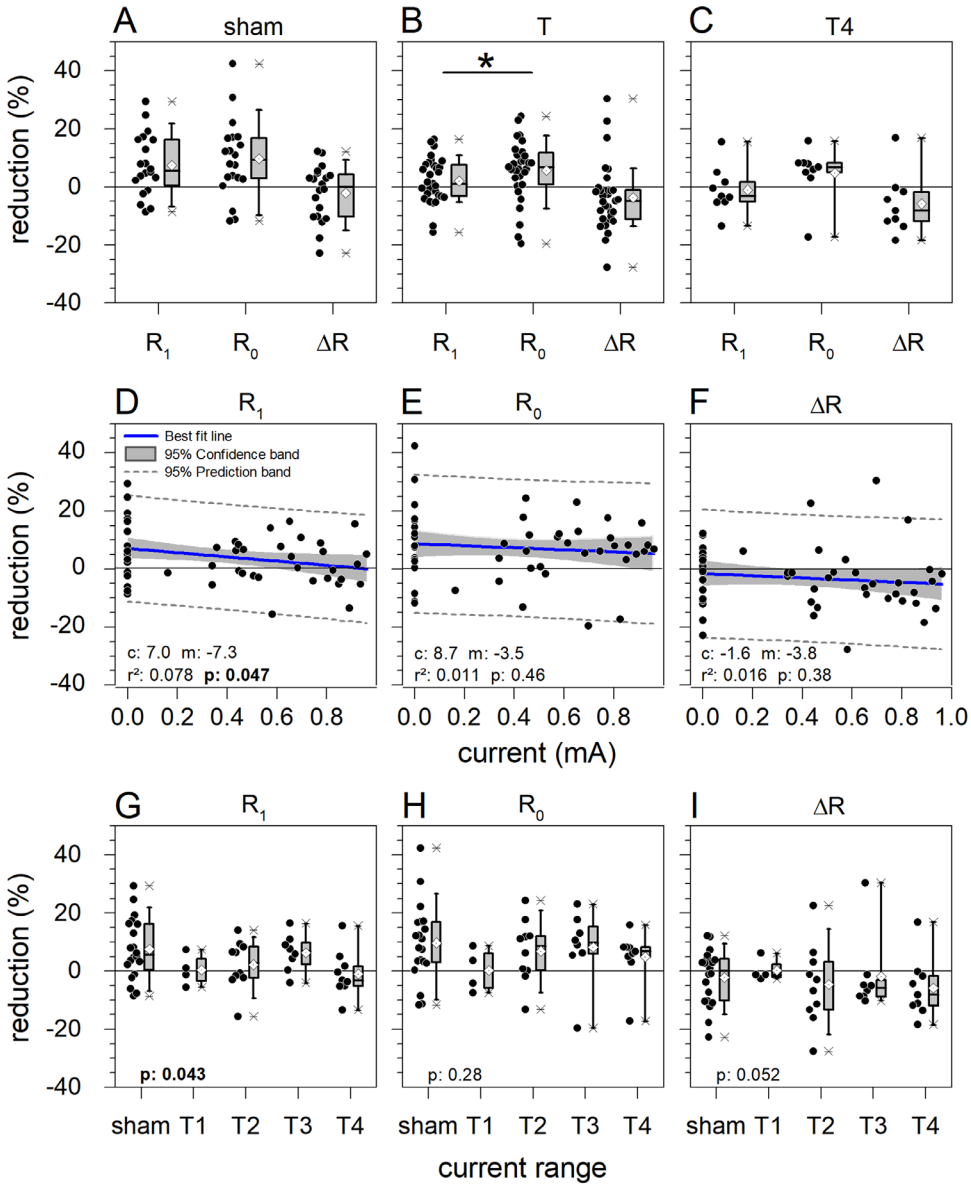

Figure 5. Percentage reduction of VFA after 1 year of treatment for target V4e. (A) Boxplot comparing R_1 (treated eye) and R_0 (untreated eyes) in the sham group. ΔR: individual interocular differences. (B) Boxplot comparing R_1 and R_0 in the TcES-treated group T. *Asterisk* indicates statistically significant difference in the distributions ($P = 0.041$, paired Wilcoxon signed rank test). (C) Boxplot comparing R_1 and R_0 in the subgroup T4 with patients stimulated with >0.8 mA. (D–F) Scatterplots showing the percentage reductions R_1, R_0 and the differences ΔR as a function of the mean current amplitude. *Blue line*: Best-fit line of linear regression; *gray area*: 95% confidence band for regression line; *gray dashed line*: 95% prediction band; c, m: intercept and slope of best-fit line. (G–I) Boxplots showing R_1, R_0, and ΔR in the different groups of ordinal current ranges. The *P* values refer to the Jonckheere–Terpstra test.

versus sham group) were done using the Mann–Whitney *U* test. To test for a linear effect of current strength, a general linear model for the slopes s of the $\log_e$VFA% courses, Δs, R_1, R_0, and ΔR with mean current strength as an independent continuous variable was fitted. To test for a (possibly nonlinear but monotone) effect of current range on visual field decline, a Jonckheere–Terpstra (nonparametric) test on R_1, R_0, and ΔR was employed.

Results of linear regression are presented descriptively using the intercept c of the regression line with the y-axis, slopes (time course: s, current strength and VFA: m), standard error, coefficient of determination (r^2), and *P* value. To compare slopes of two regression lines, a *t*-test was performed. The reductions R_1 and R_0 and difference ΔR are presented descriptively using the mean, standard deviation, median, and quartiles, as well as boxplots.

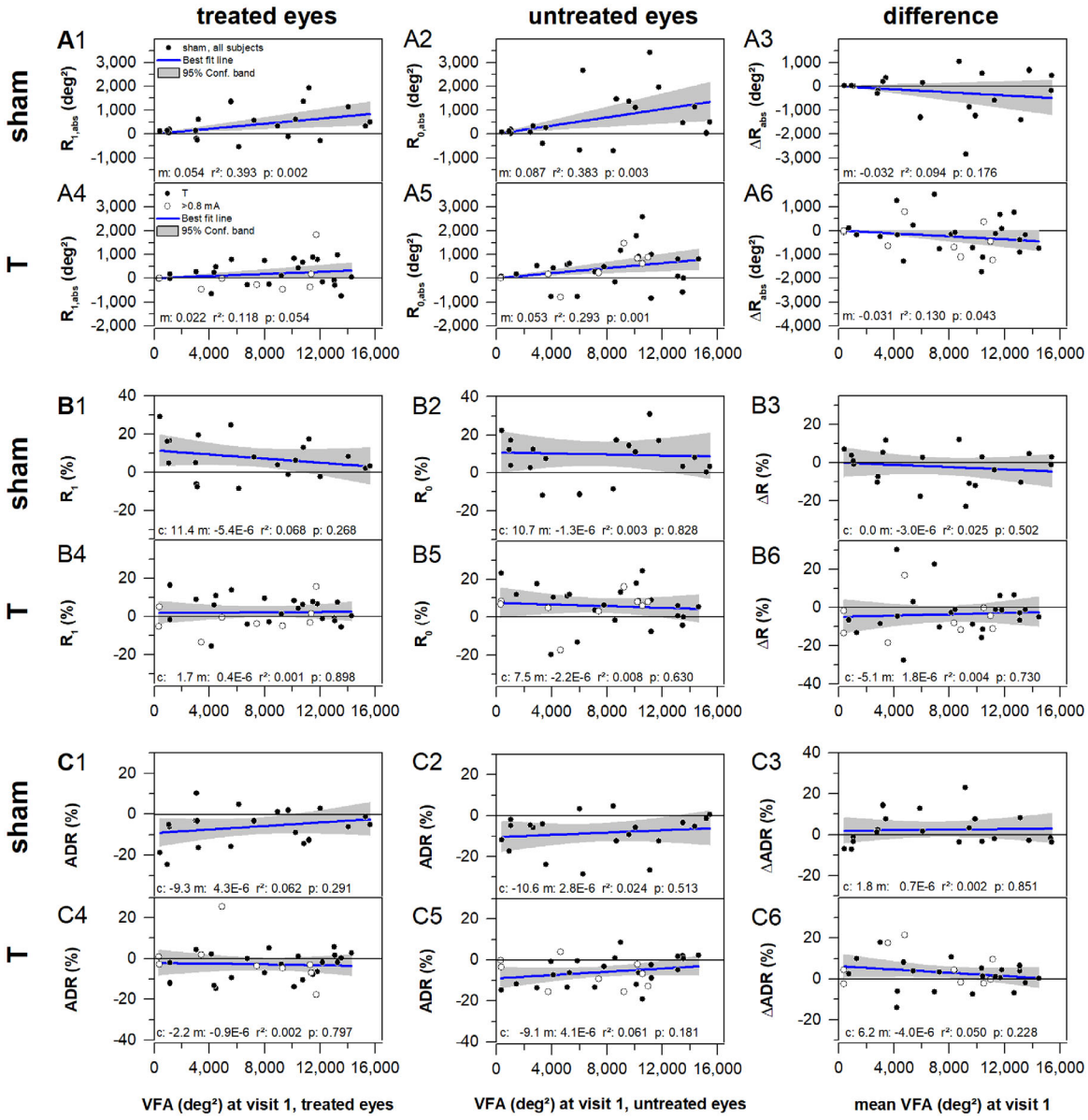

Figure 6. Evaluated parameters of the VFA progression (target V4e) in the sham group (*upper plots*) and in the TcES-treated group T (*lower plots*) with respect to baseline VFA. (A) Absolute reductions R_{abs} in the treated (A1, A4) and untreated eyes (A2, A5) and individual interocular differences ΔR_{abs} (A3, A6). (B) Relative reductions R in the treated (B1, B4) and untreated eyes (B2, B5) and individual interocular differences ΔR (B3, B6). (C) ADR calculated from the slopes of individual $\log_e$VFA courses (weeks 1–78) in the treated (C1, C4) and untreated eyes (C2, C5) and individual interocular differences ΔADR (C3, C6). *Straight blue lines* represent the best-fit line from linear regression, and the *dashed gray lines* represent the 95% confidence interval (best-fit line parameters, see Supplementary Table S3).

Results

VFA at Baseline

At baseline, 60% of treated eyes had a larger VFA (target V4e) than the untreated fellow eyes (III4e: 58%). The VFAs of the treated eyes spanned a range from 338 to 15,632 deg^2 (median, 8141 deg^2) for target V4e and from 211 to 14,871 deg^2 (median, 4255 deg^2) for target III4e.

VFA at baseline in both eyes correlated strongly (Supplementary Figs. S3A, D, V4e: $r^2 = 0.931$, III4e: $r^2 = 0.886$). Mean variability of the interocular difference in VFA (Supplementary Figs. S3C, F) was 12.9% ± 16.5% (III4e: 19.8% ± 19.3%). Test–retest variability using VFA values from screening and baseline

Table 2. Statistics of Phosphene Thresholds (EPT) of the Treated Eyes (A) and Mean Current Amplitudes for TcES Treatment (B)

	EPT (mA)				
(A) Group	Mean	SD	Q1	Median	Q3
Sham	0.401	0.214	0.309	0.375	0.425
150% EPT	0.424	0.183	0.300	0.467	0.533
200% EPT	0.336	0.110	0.267	0.300	0.420
	Current Amplitude (mA)				
(B) Group	Range	Mean	SD	Minimum	Maximum
150% EPT	—	0.603	0.243	0.163	0.960
200% EPT	—	0.660	0.189	0.340	0.922
Sham	0.0	0.000	0.000	0.000	0.000
T	—	0.634	0.213	0.163	0.960
T1	>0.0–0.4	0.300	0.092	0.163	0.358
T2	>0.4–0.6	0.488	0.056	0.435	0.580
T3	>0.6–0.8	0.701	0.062	0.615	0.786
T4	>0.8	0.884	0.053	0.804	0.960

Statistics of current amplitude refer to individual average current amplitudes applied from weeks 1 to 52. Q1, first quartile; Q3, third quartile; SD, standard deviation.

visits were 8.1% for V4e and 13.9% for III4e. Further details of the analysis of test–retest variability and interocular variability are shown in Supplementary Table S1, Supplementary Figure S2, and Supplementary Figure S3.

Phosphene Thresholds and Stimulation Strength

The individual EPTs of the treated eyes at visit 1 (Fig. 1A) span a range of 0.1 to 1.2 mA (Table 2A). The distribution of EPTs of all study groups was statistically not significantly different ($P = 0.233$). The distributions of the mean amplitudes of the administered stimulation currents in the 150% and 200% EPT groups (Table 2B, Fig. 1B) also were statistically not different ($P = 0.623$). Aggregated from both groups, the mean current amplitudes span a continuum with almost equally distributed values from 0.3 to 1.0 mA (Fig. 1C).

At baseline, there was a significant negative correlation between EPT and VFA (target V4e, Fig. 1D: $r^2 = 0.122$, $P = 0.012$; target III4e, data not shown: $r^2 = 0.154$, $P = 0.004$). Consequently, also the mean current amplitude correlated weakly but significantly with the baseline VFA (target V4e, Fig. 1E: $r^2 = 0.198$, $P = 0.012$; target III4e, data not shown: $r^2 = 0.248$, $P = 0.004$). Within the groups T2, T3, and T4, the current amplitudes were scattered over the full range of VFA.

Effect of TcES on the Time Course of VFA Progression

To elaborate whether regular TcES treatment over a year influenced the longitudinal course of VFA progression, we analyzed the averaged VFA% courses (V4e: Figs. 3A1–F1, III4e: Supplementary Figs. S4A1–F1) and the $\log_e$VFA% courses in the treated and in the untreated eyes (V4e: Figs. 3A2–F2, III4e: Supplementary Figs. S4A2–F2).

While VFA% for target V4e in placebo and untreated eyes decreased throughout the observation period, the time course of the TcES-treated eyes showed, after an initial decrease in VFA% with the same time constant as the untreated eyes, an increase from weeks 40 to 52, with a subsequent decrease after the end of the stimulation period (Fig. 3C1). In subgroup T4, VFA was stable with no decrease in both eyes until week 28 (Figs. 3E1, F1). At week 52, in the sham group, mean VFA% for target V4e was 92.5% ± 10.5% of baseline in the treated eye and 90.3% ± 13.3% in the untreated eye. In the TcES-treated group, VFA decreased to 97.9% ± 7.5% of baseline in the treated eye and 94.2% ± 10.3% in the untreated eye. In the subgroup T4, VFA was 101.0% ± 8.1% and 95.1% ± 9.0% in the treated and untreated eyes, respectively.

Linear regression was applied to the $\log_e$VFA% courses during the treatment period from weeks 1 to 52 and additionally to the courses from weeks 1 to 78 (V4e: Figs. 3A2–F2, III4e: Supplementary Figs. S4A2–F2). Within the limits of the 95% confidence intervals (Table 3), the slopes in both periods were essentially the same. Both for target V4e and for III4e and for both fitting intervals, the slope of the best-fit line for TcES-treated eyes (V4e: Fig. 3C2, III4e: Supplementary Fig. S4C2) was less steep than for placebo-treated eyes in the sham group (Fig. 3A2, Supplementary Fig. S4A2; slopes, see Table 3). In the most stimulated subgroup T4 (target V4e), there was no statistically significant linear relationship of $\log_e$VFA% of the TcES-treated eyes with time (weeks 1–52: $P = 0.34$, weeks 1–78: $P = 0.15$).

For target V4e, the slopes for treated eyes in the TcES-treated group T and in the placebo-treated sham group were statistically significant different (Table 4; only weeks 1–78: $P = 0.043$), also in the subgroup T4 (weeks 1–52: $P = 0.014$, weeks 1–78: $P = 0.002$). In T4, the slope for weeks 1 to 78 for the treated eyes was statistically significant different from the slope in the untreated fellow eyes ($P = 0.006$). The slope for untreated eyes was statistically significant less steep

Table 3. Estimated Slopes of the Logarithmic Mean VFA% Course and ADRs Calculated from Them Using Equation (1)

				Slope						
Target	Group	Fit Range, wk	Eyes	Estimate	SE	95% LCL	95% UCL	r^2	*P*	ADR, %
V4e	Sham	1–52	Treated	−0.083	0.010	−0.111	−0.055	0.943	0.001	−8.0
			Untreated	−0.128	0.015	−0.170	−0.087	0.949	0.001	−12.0
		1–78	Treated	−0.075	0.007	−0.093	−0.057	0.958	<0.001	−7.2
			Untreated	−0.106	0.013	−0.139	−0.073	0.932	<0.001	−10.1
	T	1–52	Treated	−0.051	0.016	−0.095	−0.006	0.717	0.034	−5.0
			Untreated	−0.066	0.008	−0.088	−0.045	0.948	0.001	−6.4
		1–78	Treated	−0.042	0.010	−0.069	−0.015	0.764	0.01	−4.1
			Untreated	−0.066	0.005	−0.078	−0.054	0.975	<0.001	−6.4
	T4	1–52	Treated	−0.014	0.013	−0.051	0.022	0.228	**0.34**	−1.4
			Untreated	−0.050	0.008	−0.074	−0.027	0.899	0.004	−4.9
		1–78	Treated	−0.014	0.008	−0.034	0.007	0.366	**0.15**	−1.4
			Untreated	−0.062	0.007	−0.081	−0.044	0.939	<0.001	−6.0
III4e	Sham	1–52	Treated	−0.123	0.015	−0.164	−0.083	0.947	0.001	−11.6
			Untreated	−0.128	0.028	−0.207	−0.049	0.836	0.011	−12.0
		1–78	Treated	−0.090	0.016	−0.132	−0.047	0.855	0.003	−8.6
			Untreated	−0.094	0.022	−0.151	−0.037	0.783	0.008	−9.0
	T	1–52	Treated	−0.100	0.017	−0.148	−0.052	0.891	0.005	−9.5
			Untreated	−0.097	0.008	−0.120	−0.074	0.972	<0.001	−9.2
		1–78	Treated	−0.081	0.013	−0.115	−0.047	0.881	0.002	−7.8
			Untreated	−0.083	0.008	−0.103	−0.064	0.960	<0.001	−8.0
	T4	1–52	Treated	−0.085	0.021	−0.143	−0.028	0.807	0.015	−8.1
			Untreated	−0.052	0.016	−0.097	−0.008	0.726	0.031	−5.1
		1–78	Treated	−0.067	0.015	−0.105	−0.029	0.802	0.006	−6.5
			Untreated	−0.053	0.010	−0.078	−0.028	0.855	0.003	−5.2

Time courses see corresponding Figure 3 for targets V4e and Supplementary Fig S4 for III4e. Slopes were obtained from fitting $\log_e$VFA% data of the treatment period (weeks 1–52) and additionally from fitting including data from the follow-up visit at week 78. Bold *P* values indicate slopes that are statistically not significant different from zero. The *P* values refer to testing if slopes are equal to zero (H0: slope is zero, *F* test). LCL, lower confidence limit; SE, standard error of the estimate; UCL, upper confidence limit.

in the TcES-treated group T than in the sham group (weeks 1–52: $P = 0.022$, weeks 1–78: $P = 0.021$). No significant differences in the slopes between groups and eyes were found for target III4e (Supplementary Fig. S4; *P* values, see Table 4).

The ADR for the TcES-treated eyes calculated from the slope of the $\log_e$VFA% course in the fitting interval weeks 1 to 78 (group T in Table 3) was smaller than the ADR of the placebo-treated eyes, both for target V4e (−4.1% vs. −7.2%) and for target III4e (−7.8% vs. −8.6%). It was also smaller than the ADR for untreated fellow eyes (V4e: −4.1% vs. −6.4%, III4e: −7.8% vs. −8.0%). In the subgroup T4, the V4e ADR of the treated eyes was −1.4% compared to −6.0% in the untreated eyes (III4e: −6.5% vs. −5.2%). ADRs for fitting interval weeks 1 to 52 can be seen in Table 3.

The slopes of the individual $\log_e$VFA courses for V4e showed a slight, statistically not significant linear dependence on the mean current strength (Figs. 4A–C) for both the treated eyes ($r^2 = 0.05$, $P = 0.12$) and the untreated eyes ($r^2 = 0.03$, $P = 0.25$). No tendency for a correlation of slopes with current amplitude was found for III4e (Figs. 4D–F, treated eyes: $r^2 = 0.0$, $P = 0.67$; untreated eyes: $r^2 = 0.0$, $P = 0.83$).

Reduction of VFA After 1 Year

In a further step, we analyzed the reduction of VFA at the end of the stimulation period independently of the time course between onset and termination of stimulation. The individual percentage reductions in the treated and untreated fellow eyes were obtained

Table 4. Significance of Difference Between $\log_e$VFA% Courses Shown in Figure 3 and Supplementary Figure S4

			Untreated Fellow Eyes		Sham, Treated Eye		Sham, Untreated Eye	
Target	Eye	Group	Weeks 1–52	Weeks 1–78	Weeks 1–52	Weeks 1–78	Weeks 1–52	Weeks 1–78
V4e	Treated	T	0.50	0.09	0.17	**0.043**	—	—
		T4	0.08	**0.006**	**0.014**	**0.002**	—	—
		Sham	—	—	—	—	0.07	0.09
	Untreated	T	—	—	0.26	0.33	**0.022**	**0.021**
		T4	—	—	0.62	0.25	**0.010**	**0.031**
III4e	Treated	T	0.88	0.90	0.37	0.68	—	—
		T4	0.59	0.81	0.22	0.34	—	—
		Sham	—	—	—	—	0.88	0.89
	Untreated	T	—	—	0.20	0.71	0.35	0.65
		T4	—	—	0.26	0.53	0.27	0.51

P values are given for comparing slopes obtained from fitting data of the treatment period (weeks 1–52) and for fitting including data from the follow-up visit at week 78. The P values refer to testing if slopes of compared regression lines are different (H0: slopes are equal, *t*-test). Bold *P* values indicate statistically significantly different slopes.

by dividing absolute reduction at visit 12 by the initial VFA value at visit 1 (Fig. 2C).

For target V4e, in the sham group, the mean percent reductions R_1 and R_0 were 7.5% ± 10.5% and 9.7% ± 13.3% (mean ± SD), with a mean of the interocular difference ΔR of −2.2% ± 9.5% and a zero median of the difference (Table 5 and Fig. 5A). In the treated group T, the mean R_1 and R_0 were 2.1% ± 7.7% and 5.8% ± 10.3%, with a mean difference ΔR of −3.7% ± 11.6% and a median of the difference of −4.8% (Fig. 5B). The two distributions R_1 and R_0 were statistically significantly different ($P = 0.013$), and the difference between R_1 in group T and in the sham group missed statistical significance ($P = 0.103$). On average, R_1 was 63.8% less in the TcES-treated eyes than R_0 in the untreated fellow eyes and 72.0% less than R_1 in the placebo-treated eyes. In the sham group, R_1 was 29.3% less than R_0. In the subgroup T4, R_1 was −1.0% ± 8.1%, R_0 was 4.9% ± 9.0%, and ΔR was −5.9% ± 10.3%, with a median difference of −8.2% (Fig. 5C). The difference in the two distributions R_1 and R_0 missed statistical significance ($P = 0.098$), whereas R_1 was statistically significantly different from R_1 in the sham group ($P = 0.036$).

There was a significant linear relationship ($r^2 = 0.078$, $P = 0.047$) between the reduction R_1 in the treated eyes and the current amplitude (Fig. 5D) for target V4e. The line of best fit indicated zero reduction ($R_1 = 0$) at stimulation with 0.9 mA. No significant linear correlation with current amplitude was found for the reduction R_0 in the untreated eyes ($P = 0.46$) and for the difference ΔR ($P = 0.38$). In the ordinal model (Figs. 5G, I), the nonparametric Jonckheere–Terpstra test confirmed a significant decrease in R_1 with increasing current strength ($P = 0.043$) and a tendency for ΔR ($P = 0.052$). The number of pairs of eyes in which the reduction of VFA (target V4e) in the treated eye was smaller than in the untreated eye (ΔR < 0 in Fig. 5I) was 50% in the placebo-treated sham group (10 of 20); 77% in the aggregated TcES-treated groups T1, T2, and T3 (17 of 22); and 89% (8 of 9) in subgroup T4.

For target III4e, no significant difference between R_1 and R_0 could be found (Table 5, Supplementary Figs. S5A–C). The linear correlations between the reductions and the current strength were statistically not significant (*P* values, see Supplementary Figs. S5D–F). The Jonckheere–Terpstra test revealed a marginally significant correlation of ΔR with increasing current ranges ($P = 0.11$, Supplementary Fig. S5I).

Dependence of TcES Effects on Initial VFA

To test whether the TcES effect on the decline of the VFA depended on the severity of RP at the onset of the treatment, we correlated both the individual reductions of VFA loss and the individual ADR with the baseline VFA. For results of linear regression analysis, see Supplementary Table S3 and values added to Figure 6 (V4e) and Supplementary Figure S6 (IIIe). For target V4e, the linear regression analysis revealed a statistically significant linear positive correlation of the absolute reductions in the treated eyes ($R_{1,abs}$, sham: $P = 0.002$, T: $P = 0.054$) and untreated eyes ($R_{0,abs}$, sham: $P = 0.003$, T: $P = 0.001$) with the baseline VFA in the respective eyes (Fig. 6A). The slope m of the best-fit lines for $R_{1,abs}$ and $R_{0,abs}$ was smaller in the TcES-treated group than in the sham group, and the slope for the interocular difference was

Table 5. Statistics of the Percentage Reduction of VFA at the End of the 12-Month Treatment Period in the Different Groups of Stimulation Strength

Target	Group	Parameter	Mean	SD	Q1	Median	Q3	*P*
V4e	Sham	R_1	0.075	0.105	0.005	0.056	0.162	0.52
		R_0	0.097	0.133	0.030	0.095	0.169	
		ΔR	−0.022	0.095	−0.103	−0.000	0.043	
	T	R_1	0.021	0.077	−0.032	0.011	0.077	**0.013**
		R_0	0.058	0.103	0.007	0.067	0.118	
		ΔR	−0.037	0.116	−0.112	−0.048	−0.012	
	T1	R_1	0.004	0.054	−0.034	−0.001	0.042	0.88
		R_0	0.002	0.074	−0.058	−0.003	0.062	
		ΔR	0.002	0.040	−0.020	−0.013	0.024	
	T2	R_1	0.022	0.085	−0.023	0.028	0.083	0.28
		R_0	0.069	0.108	0.002	0.086	0.120	
		ΔR	−0.047	0.139	−0.134	−0.049	0.030	
	T3	R_1	0.063	0.063	0.023	0.067	0.099	0.20
		R_0	0.082	0.126	0.059	0.098	0.153	
		ΔR	−0.019	0.133	−0.087	−0.058	−0.030	
	T4	R_1	−0.010	0.081	−0.051	−0.032	0.016	0.10
		R_0	0.049	0.090	0.050	0.067	0.082	
		ΔR	−0.059	0.103	−0.118	−0.082	−0.018	
III4e	Sham	R_1	0.104	0.165	0.007	0.069	0.155	0.60
		R_0	0.086	0.214	−0.033	0.077	0.210	
		ΔR	0.018	0.172	−0.064	0.030	0.097	
	T	R_1	0.051	0.124	0.004	0.054	0.123	0.31
		R_0	0.077	0.180	−0.019	0.099	0.168	
		ΔR	−0.026	0.127	−0.143	−0.023	0.072	
	T1	R_1	0.024	0.073	−0.024	0.019	0.071	0.63
		R_0	0.002	0.114	−0.065	−0.035	0.070	
		ΔR	0.022	0.121	−0.056	0.042	0.100	
	T2	R_1	−0.008	0.149	−0.097	0.039	0.078	0.49
		R_0	0.018	0.218	−0.019	0.063	0.126	
		ΔR	−0.026	0.117	−0.135	−0.028	0.050	
	T3	R_1	0.135	0.111	0.052	0.116	0.197	0.31
		R_0	0.189	0.192	0.038	0.168	0.315	
		ΔR	−0.054	0.136	−0.173	−0.053	0.019	
	T4	R_1	0.053	0.092	−0.029	0.057	0.082	0.73
		R_0	0.076	0.108	0.026	0.114	0.162	
		ΔR	−0.023	0.146	−0.191	0.031	0.089	

See Figure 5 (V4e) and Supplementary Figure S5 (III4e). R_1, R_0 reduction of VFA% in the treated and untreated eye, respectively. $\Delta R = R_1 - R_0$. The *P* values refer to testing if R_1 and R_0 are equal (H_0: $R_1 = R_0$, Wilcoxon signed rank test).

the same in both groups (slopes, see Supplementary Table S3). For target III4e (Supplementary Fig. S6A), no interocular difference in the TcES-treated group was found. No significant correlation with the baseline VFA was found for the percentage reductions (Fig. 6B, Supplementary Fig. S6B), the ADR (Fig. 6C, Supplementary Fig. S6C), and their respective interocular differences for both V4e and III4e (*P* values, see Supplementary Table S3). The slopes of the $\log_e$VFA courses and the percentage reductions also did not correlate significantly with the interocular difference in VFA at baseline ($P > 0.05$, data not shown).

Ocular Adverse Events

To investigate whether TcES shows a current-dependent effect on safety parameters, we analyzed the frequency of occurrence of ocular adverse events

Table 6. Nature and Number of Ocular AEs Based on Their Assignment to Treatment Groups and Causality

	Group						Device-Related Ocular AEs			
Ocular AE	Sham	T	T1	T2	T3	T4	Certain	Probable	Possible	Unlikely
Dry eye symptom	2	38	3	13	13	9	33	3	3	1
Ocular discomfort	2	1		1						3
Ocular pain	1	3		1		2	3			1
Transient visual disturbance	1	2			1	1			1	1
Ocular pain during EPT detection	2						2			
Cataract surgery		2			2					
Increased tear production		2				2			2	
Conjunctivitis		1			1					
Corneal erosion		1				1				
Itching and burning sensation		1			1					1
Macular edema	1									
Subjective visual decrease	1									
Number of AEs	10	51	3	15	18	15	38	3	6	7
Patients with AEs	7	24	2	7	9	6	24	3	4	5
Number of patients total	20	32	4	10	9	9				
% patients with AEs per group	*35%*	*75%*	*50%*	*70%*	*100%*	*67%*				
Patients with dry eye symptom	2	23	2	7	8	6				
% patients with dry eye symptoms per group	*10%*	*72%*	*50%*	*70%*	*89%*	*67%*				

All patients who completed the study per protocol are included. The row "% patients with AEs per group" shows the percentage of patients in the respective group that experienced at least one ocular AE.

(AEs). A description and the number of all ocular AEs occurring in the study in all 52 patients (who all completed the study per protocol) are shown in Table 6. Seventy-five percent of TcES-treated patients had at least one AE, compared with 35% in the sham group. In the TcES-treated group, there is no correlation between frequency of occurrence of the symptoms and current intensity.

The main ocular AE was "dry eye symptom," which occurred 2 times in 2 patients in the sham group (10% of patients) and 38 times in 23 patients (72%) in the TcES-treated groups (T1–T4). Adverse events were generally mild ($n = 58$). The relationship to the device was "certain" in 38 cases (33 of them were dry eye symptoms), "probable" in 3 cases, "possible" in 6 cases, and "unlikely" in 7 cases, and no relationship to the device was assigned to 7 AEs. The outcome was described as "recovered" in 42 cases, "improved" in 18 cases, and "unchanged" in 1 case (mild ocular discomfort in the sham group).

Discussion

Any therapy for RP should reverse, halt, or at least slow the progression of the disease. Here, we provide evidence that TcES can slow the visual field loss in patients with RP. Central to our argumentation is that the slowing effect of TcES on VFA shows a statistically significant correlation to stimulation intensity, as demonstrated by a dose–response relationship between applied current and progression of visual field. To prove the current-dependent effect of TcES, we expanded the analysis of the VFA data of our previous EST2 trial[21] and included both the sham group and fellow-eye controls. This allowed both interocular comparison of the treatment effects of the monocularly applied current and comparing the effects in the TcES-treated group with the natural changes in the sham group.

Slowing of the Annual Decline of VFA by TcES

ADR was determined by different analyses of the VFA course. To investigate the temporal structure of the progression of differently sized visual fields, the time series of the VFA values were normalized to their initial value and then averaged. In this way, the large variability of the individual courses had been smoothed and possible treatment-specific influences on the temporal structure of the VFA progression became visible. We found a statistically significant slowing

effect of TcES treatment on the visual field decline (Table 3, Table 4). In the TcES-treated eyes, the mean ADR for target V4e (−4.1%) was statistically significantly lower than in the placebo-treated eyes (−7.2%). ADRs in the placebo-treated eyes in the sham group are comparable to ADRs reported in the literature, with values from −7.5% to −12.0% for target V4e.[4–6] The ADR of the untreated fellow eyes in the TcES-treated group was smaller than the ADRs of untreated and placebo-treated eyes in the sham group, indicating a contralateral attenuated slowing effect of unilateral stimulation. This could explain the flat time course of VFA of the untreated eyes in subgroup T4 (Fig. 3F1, Supplementary Fig. S4F1). It could also explain the weak, nonsignificant current dependence of the slopes of the individual $\log_e$VFA courses in untreated eyes (Fig. 4B). Mean test–retest variability was 8% for the V4e target and 14% for the III4e target, lower than published values for the semiautomatic kinetic perimetry.[36] The interocular differences contributed more to the statistical variability than the intervisit differences. At baseline, interocular variability was 13% for target V4e and 20% for III4e. The distinctly larger variabilities for target III4e may explain the lack of significance of the results.

Dose–Response Dependency of TcES Effects

The ADR of treated eyes was lowest in the subgroup stimulated with currents greater than 0.8 mA (Table 3). However, the slopes of the individual $\log_e$VFA courses in treated eyes showed only a weak, statistically nonsignificant correlation with current intensity (Fig. 4A). In addition to the large variation of the individual values, the marginal significance may also be due to a possibly delayed onset of the treatment effect on the progression course. Assuming an exponential decline, the slope of the best-fit line from the linear regression analysis of the $\log_e$VFA progression is the suitable measure to describe the longitudinal course of the VFA, as shown by the semi-log plots in Figure 3 and Supplementary Figure S1. However, if stimulation causes the progression to gradually slow down, the curve of visual field decline will over time deviate more and more from the course of a simple decreasing e-function. In the best case, the visual field might even increase again after some time, as indicated by the course of the VFA of the TcES-treated eyes shown in Figure 3 C. If so, calculating the ADR from the slope from the regression line over the entire study period will result in an underestimation of the final effect size. This argument is supported by the model-independent VFA reduction within a year (R_1 in Table 5) that was smaller than the annual decline derived from the $\log_e$VFA% courses of TcES-treated eyes (Table 3).

The use of percentage reductions of the VFA at a prespecified time point has the advantage of being independent of the mathematical form of the changes over time—in particular, whether VFA declines exponentially or not. Its disadvantage is the reliance on values at a single time point and therefore greater sensitivity to variability. Conversely, the use of linear regression of $\log_e$VFA has the advantage of using more measurements and is thus less sensitive to variability, but it has the disadvantage of assuming an exponential decline, which may not be valid.

Assessing a potential dose–response relationship, we found a significant linear correlation between the reduction R_1 in the treated eyes and the current strength yielding zero reduction at 0.9 mA (Fig. 5F). In the range of 0.8 to 1.0 mA, 6 of 9 treated eyes (66%) even had an increase of the VFA, compared to 1 of 9 (11%) untreated fellow eyes and 5 of 20 (25%) placebo-treated eyes. This suggests that TcES treatment is most effective above 0.8 mA. However, this study had a small sample size, and larger trials are needed to confirm the effective dose for TcES. Not all patients with RP should be treated indiscriminately with 0.8 to 1.0 mA. In practice, the stimulation dose must be adjusted to the individual tolerance level at which patients can withstand TcES for 30 minutes. Limits for safe current densities at the ocular surface must also be considered.

From results of preclinical experiments, dose effects in clinical TcES application can be expected.[25,26,29] An important role in the neuroprotective effects of ocular stimulation has been attributed to the Müller cells (MCs). Enayati et al.[25] found in cultured MCs from a mouse model that electrical stimulation enhanced the MC proliferation and expression of photoreceptor progenitor cell markers via calcium signaling, which is mediated by voltage-gated calcium channels. As the triggering of Ca^{2+} channels is linked with the activation of subcellular biochemical cascades related to neuroprotective pathways in the retina,[25] we postulate that TcES dose-dependently activates subcellular pathways, which leads to cellular and thus potentially clinically relevant protective effects in the retina.

Onset and Persistence of TcES Effect

The effect of TcES on the visual field loss has been investigated in only a few studies, and comparison of results is difficult because the protocols and methods used to determine the changes in visual fields were different. Schatz et al.[33] found in a randomized and controlled trial with 24 patients a significant increase of the mean VFA (target III4e) by 9% after

6 weeks of consecutive stimulation with 150% EPT. The improvement was still present at the follow-up visit 11 weeks after termination of the stimulation. Bittner and Seger[32] reported on the longevity of effects for three patients with RP who received 0.75 mA. They were positive responders from their previous randomized controlled trial of TcES,[30] in which four of seven patients showed improvement in VFA (target III4e) and corresponding retinal area, respectively, after six stimulations (current amplitude 0.75 mA) at 1-week intervals. Sinim Kahraman and Oner[22] found a similar result in a large observational trial with 101 treated and 100 untreated patients with RP. They observed a significant improvement by 1.67 dB of the mean deviation of the visual field from the age-corrected norm in the central 30° of the visual field after only 4 weeks of stimulation with 150% EPT. The improvement attenuated partially 4 months after cessation of stimulation but remained at a higher level than at baseline.

Improvements that occurred within a few weeks of onset of treatment were not observed in the EST2 trial due to the design of the study. Here, the first measurement took place at 16 weeks after stimulation onset. Short-term effects of TcES therapy are not yet well explored. In a 6-month study, Della Volpe-Waizel et al.[23] found an increased oxygen consumption by retinal cells, suggesting an increased metabolism by TcES. This may indicate an initial boost leading to measurable improvements of VFA and visual acuity.

In the EST2 study, the VFA of TcES-treated eyes appeared to increase toward the end of the 1-year treatment period and then, after cessation of stimulation, to decrease with the time constant of natural decay (Fig. 3C). The VFA changes after 1 year to the control visit after 1.5 years corresponded approximately to the course of progression in the sham group and in the untreated fellow eyes. This observation is consistent with the finding of Sinim Kahraman and Oner[22] that the protective effects of TcES are transient and suggests that the degenerative processes resume when stimulation is ceased. Hence, chronic TcES is required to permanently delay photoreceptor degeneration. However, whether the peculiar pattern in the averaged VFA% time courses is indicative of a treatment effect or due to variability in the data remains to be shown.

Dependency of TcES Effect on Disease Stage

Our study provided no evidence that the efficacy of treatment depends on the initial extent of VFA loss. The percentage reductions R_1, the ADR calculated from the slopes of the $\log_e$VFA courses, and the interocular differences in ΔR and in ADR (represented by Δs) did not correlate significantly with the VFA at baseline (Supplementary Table S3, Fig. 6). This result is consistent with an exponentially decreasing function as it is used to describe the VFA progression in RP. For exponential decline over time, the absolute annual decline depends on the initial value at the beginning of the observation period, whereas the percentage decline is independent of the baseline value. However, since we only evaluated data from the kinetic perimetry, no generally valid statement can be made as to whether the efficacy of TcES treatment depends on the severity of the disease.

A limitation of the trial protocol might be that the worse eyes were intended to be selected for TcES treatment. But, in fact, no systematic pattern for the interocular difference in VFA of treated versus untreated eyes at baseline and no significant correlation of the interocular variability with baseline VFA were found (Supplementary Table S2 and Supplementary Fig. S3). The outcome parameter percentage reductions and ADR in the treated and untreated eyes also did not correlate significantly with the interocular difference in initial VFA.

The Octopus perimeter performs a planimetric calculation of the VFA. A conversion into retinal areas considering the spherical aspects and the optical properties of the eye does not take place.[36] Thus, there is a possibility that the evaluated VFA values do not reflect the true size relations of the corresponding retinal area, especially of peripheral areas.[37] In our case, however, this is unlikely to cause error because we did not evaluate the absolute VFA but considered relative longitudinal changes of the visual field with respect to the baseline value.

Electrically Evoked Phosphenes and Stimulation Strength

In TcES studies, the amplitude of the stimulation current was usually chosen as a multiple of the EPT, most commonly 150% and 200% EPT.[20–22,33] The EPT is a subjective measure that varies greatly between patients (Fig. 1A) and spans a wide range of values.[34] It depends on many individual factors, including the cause and the state of degeneration of the retina.[34,38] Thus, defining individual stimulation strength as a factor of individual EPT necessarily results in a broad distribution of current amplitudes. If cellular effects of TcES depend on the stimulus strength and grouping patients according to a multiple of EPT, group differences may be lost due to the averaging of measured dose-dependent variables within groups. The effects are further attenuated when

the current amplitude is adjusted to EPTs several times, as has been done in the EST2 trial. This may at least partially explain the high variability of the obtained data and the inconsistent results from the past studies.

We thus conclude that stimulation current should not be defined based on a multiple of EPT when dose-dependent effects of TcES are to be investigated. In clinical trials, dose dependency of TcES effects could be explored by comparing groups receiving low, medium, and high doses of stimulation.

Safety of the TcES Application

All conducted and analyzed clinical studies uniformly demonstrate the safety of using TcES therapy in outpatient settings and in performing therapy at home.[39] In the trial presented here, the observed side effects of TcES (Table 6) were generally mild and transient in nature. The most frequent side effect was dry eye symptoms during treatment, which could be resolved by artificial tear application in less than 1 day.[21] The frequency of occurrence did not depend on the stimulus intensity. These findings are in line with the results from previous trials.[20,22] In the EST2 trial, artificial tears were not used in asymptomatic cases. However, in regular therapeutic practice, it has since been recommended to use artificial tears immediately before and during TcES treatment to reduce the occurrence of dry eye symptoms.

Limitations of the A Posteriori Analysis

The EST2 study has not originally been designed to assess a dose–response relation. Thus, the a posteriori analysis of the data and the results are subject to several limitations. The distributions of ADR and reductions after 1 year derived from the VFA measurements show high variability. The large standard deviations limit the statistical power to detect effects. This reflects the known measurement inaccuracies of kinetic perimetry, the large differences in individual progression courses, and the short observation period of 1 year with respect to the ADR. The stimulus intensity also contributes to the variability of the data. Individual current amplitudes were changed several times during treatment, leading to different effects of TcES in different time intervals. Additionally, only a small fraction of patients received stimulation with the highest amplitudes, which might be necessary to cause a measurable effect in the visual field progression. It cannot be excluded that the patients noticed which eye was stimulated and which was the control eye. This possible unmasking could lead to a perceptual bias in the visual field measurement. When planning future studies, genetic cause and stage of the disease, treatment duration, and stimulation strength should be considered accordingly to keep the variability of the data low. Emphasis must be placed on the accurate measurement of VFA.

Summary and Conclusion

The results of the a posteriori analysis support the hypothesis that the annual visual field decline in RP can be significantly slowed by regular use of TcES. For the first time, a dose–response relation of TcES has been demonstrated based on data from a prospective, randomized clinical trial. The beneficial effect of TcES did not correlate with baseline VFA. This opens the possibility of not only applying the TcES therapy very early in the course of the disease, when the limitations of vision are still small, but also preserving visual function for longer in moderate to severe disease stages. A halving of the annual decline of the VFA from –7.0% to –3.5% approximately doubles the half-life of visual field loss from 10 years to 20 years. Starting the therapy early after disease onset would give the chance to significantly delay the onset of serious vision loss and durably improve the quality of life of patients with RP.

In conclusion, the results provide evidence that TcES is an effective and safe method to slow disease progression in RP and offers potential to preserve vision after onset of the disease. Further studies are needed to confirm the effectiveness of TcES treatment on a multiyear time scale.

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References

1. Verbakel SK, van Huet RAC, Boon CJF, et al. Non-syndromic retinitis pigmentosa. *Prog Retin Eye Res*. 2018;66:157–186.
2. Prem Senthil M, Khadka J, Pesudovs K. Seeing through their eyes: lived experiences of people with retinitis pigmentosa. *Eye*. 2017;31:741–748.
3. Massof RW, Finkelstein D. A two-stage hypothesis for the natural course of retinitis pigmentosa. *Adv Biosci*. 1987;62:29–58.

4. Massof RW, Dagnelie G, Benzschawel T, Palmer RW, Finkelstein D. First order dynamics of visual field loss in retinitis pigmentosa. *Clin Vis Sci*. 1990;5:1–26.
5. Xu M, Zhai Y, MacDonald IM. Visual field progression in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2020;61:56.
6. Holopigian K, Greenstein V, Seiple W, Carr RE. Rates of change differ among measures of visual function in patients with retinitis pigmentosa. *Ophthalmology*. 1996;103:398–405.
7. Grover S, Fishman GA, Anderson RJ, Alexander KR, Derlacki DJ. Rate of visual field loss in retinitis pigmentosa. *Ophthalmology*. 1997;104:460–465.
8. Ross M, Ofri R. The future of retinal gene therapy: evolving from subretinal to intravitreal vector delivery. *Neural Regen Res*. 2021;16:1751–1759.
9. Wang Y, Tang Z, Gu P. Stem/progenitor cell-based transplantation for retinal degeneration: a review of clinical trials. *Cell Death Dis*. 2020;11:793.
10. McClements ME, Staurenghi F, MacLaren RE, Cehajic-Kapetanovic J. Optogenetic gene therapy for the degenerate retina: recent advances. *Frontiers in Neuroscience*. 2020;14:570909.
11. Allen PJ. Retinal prostheses: where to from here? *Clin Exp Ophthalmol*. 2021;49:418–429.
12. Maguire AM, Bennett J, Aleman EM, Leroy BP, Aleman TS. Clinical perspective: treating RPE65-associated retinal dystrophy. *Mol Ther*. 2021;29:442–463.
13. Talib M, Boon CJF. Retinal dystrophies and the road to treatment: clinical requirements and considerations. *Asia Pac J Ophthalmol (Phila)*. 2020;9:159–179.
14. Georgiou M, Fujinami K, Michaelides M. Inherited retinal diseases: therapeutics, clinical trials and end points—a review. *Clin Exp Ophthalmol*. 2021;49:270–288.
15. Pardue MT, Allen RS. Neuroprotective strategies for retinal disease. *Prog Retin Eye Res*. 2018;65:50–76.
16. Tao Y, Chen T, Liu B, et al. The transcorneal electrical stimulation as a novel therapeutic strategy against retinal and optic neuropathy: a review of experimental and clinical trials. *Int J Ophthalmol*. 2016;9:914–919.
17. Sehic A, Guo S, Cho KS, Corraya RM, Chen DF, Utheim TP. Electrical stimulation as a means for improving vision. *Am J Pathol*. 2016;186:2783–2797.
18. Rahmatnejad K, Ahmed OM, Waisbourd M, Katz LJ. Non-invasive electrical stimulation for vision restoration: dream or reality? *Exp Rev Ophthalmol*. 2016;11:325–327.
19. Fu L, Lo AC, Lai JS, Shih KC. The role of electrical stimulation therapy in ophthalmic diseases. *Graefes Arch Clin Exp Ophthalmol*. 2015;253:171–176.
20. Jolly JK, Wagner SK, Martus P, et al. Transcorneal electrical stimulation for the treatment of retinitis pigmentosa: a multicenter safety study of the OkuStim(R) system (TESOLA-Study). *Ophthalmic Res*. 2020;63:234–243.
21. Schatz A, Pach J, Gosheva M, et al. Transcorneal electrical stimulation for patients with retinitis pigmentosa: a prospective, randomized, sham-controlled follow-up study over 1 year. *Invest Ophthalmol Vis Sci*. 2017;58:257–269.
22. Sinim Kahraman N, Oner A. Effect of transcorneal electrical stimulation on patients with retinitis pigmentosa. *J Ocul Pharmacol Ther*. 2020;36:609–617.
23. Della Volpe-Waizel M, Zuche HC, Muller U, Rickmann A, Scholl HPN, Todorova MG. Metabolic monitoring of transcorneal electrical stimulation in retinitis pigmentosa. *Graefes Arch Clin Exp Ophthalmol*. 2020;258:79–87.
24. Liu J, Tong K, Lin Y, et al. Effectiveness of microcurrent stimulation in preserving retinal function of blind leading retinal degeneration and optic neuropathy: a systematic review. *Neuromodulation*. 2021;24(6):992–1002.
25. Enayati S, Chang K, Achour H, et al. Electrical stimulation induces retinal muller cell proliferation and their progenitor cell potential. *Cells*. 2020;9:18.
26. Ni YQ, Gan DK, Xu HD, Xu GZ, Da CD. Neuroprotective effect of transcorneal electrical stimulation on light-induced photoreceptor degeneration. *Exp Neurol*. 2009;219:439–452.
27. Morimoto T, Miyoshi T, Sawai H, Fujikado T. Optimal parameters of transcorneal electrical stimulation (TES) to be neuroprotective of axotomized RGCs in adult rats. *Exp Eye Res*. 2010;90:285–291.
28. Yu H, Enayati S, Chang K, et al. Noninvasive electrical stimulation improves photoreceptor survival and retinal function in mice with inherited photoreceptor degeneration. *Invest Ophthalmol Vis Sci*. 2020;61:5.
29. Morimoto T, Fujikado T, Choi JS, et al. Transcorneal electrical stimulation promotes the survival of photoreceptors and preserves retinal function in Royal College of Surgeons rats. *Invest Ophthalmol Vis Sci*. 2007;48:4725–4732.
30. Bittner AK, Seger K, Salveson R, et al. Randomized controlled trial of electro-stimulation therapies to modulate retinal blood flow and visual function in retinitis pigmentosa. *Acta Ophthalmol*. 2018;96:e366–e376.

31. Kurimoto T, Oono S, Oku H, et al. Transcorneal electrical stimulation increases chorioretinal blood flow in normal human subjects. *Clin Ophthalmol*. 2010;4:1441–1446.
32. Bittner AK, Seger K. Longevity of visual improvements following transcorneal electrical stimulation and efficacy of retreatment in three individuals with retinitis pigmentosa. *Graefes Arch Clin Exp Ophthalmol*. 2018;256:299–306.
33. Schatz A, Röck T, Naycheva L, et al. Transcorneal electrical stimulation for patients with retinitis pigmentosa: a prospective, randomized, sham-controlled exploratory study. *Invest Ophthalmol Vis Sci*. 2011;52:4485–4496.
34. Naycheva L, Schatz A, Rock T, et al. Phosphene thresholds elicited by transcorneal electrical stimulation in healthy subjects and patients with retinal diseases. *Invest Ophthalmol Vis Sci*. 2012;53:7440–7448.
35. Martin Bland J, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;327:307–310.
36. Barnes CS, Schuchard RA, Birch DG, et al. Reliability of semiautomated kinetic perimetry (SKP) and Goldmann kinetic perimetry in children and adults with retinal dystrophies. *Transl Vis Sci Technol*. 2019;8:36.
37. Bittner AK, Iftikhar MH, Dagnelie G. Test-retest, within-visit variability of Goldmann visual fields in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2011;52:8042–8046.
38. Gekeler F, Messias A, Ottinger M, Bartz-Schmidt KU, Zrenner E. Phosphenes electrically evoked with DTL electrodes: a study in patients with retinitis pigmentosa, glaucoma, and homonymous visual field loss and normal subjects. *Invest Ophthalmol Vis Sci*. 2006;47:4966–4974.
39. Perin C, Vigano B, Piscitelli D, Matteo BM, Meroni R, Cerri CG. Non-invasive current stimulation in vision recovery: a review of the literature. *Restor Neurol Neurosci*. 2020;38:239–250.