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The effect of transcorneal electrical stimulation in visual acuity: Retinitis pigmentosa

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ABSTRACT

Transcorneal Electrical Stimulation (TES) was applied to a group of volunteer patients suffering from Retinitis Pigmentosa (RP), in order to investigate the effect of TES in Visual Acuity (VA). 28 partial blind patients with diagnosis of classic RP, Usher syndrome I and/or II were stimulated transcornealy, during a period of 52 weeks using a non conventional waveform, only in the lowest visually capable eye. The proposed waveform has been modeled from the natural response of human retina and delivered by means of an adaptive generator designed and built for tissue stimulation. Statistical results show the improvement of average VA or at least the contention of the disease natural progress. Categorized analysis of results indicates the same effect that if the age of patients, time since diagnosis and genetic disorder variation (classic RP, Usher syndrome I and/or II) are considered, in this case clinical and electrophysiological follow-up parameters were statistically analyzed in order to know the effect of TES. General results yield an improvement of 48.15% in the average of VA for stimulated eyes against an average degreasing of −8.06% in the same scale, with respect to their basal condition before the start of the experiment.

Keywords: Transcorneal Electrical Stimulation; Retinitis Pigmentosa; Adaptive Waveform Model; Visual Acuity

1. INTRODUCTION

For most of the degenerative retinal and optic nerve diseases, there is no satisfactory treatment to reverse or even stop the course of degeneration. As a result, several million people worldwide become blind every year, however, TES has been used for the treatment of "amblyopia and amauroses", for "retino-choroiditis with pigment infiltration", "glaucoma" and "white optic atrophy" [1]. Recent studies suggest that Transcorneal Electrical Stimulation (TES) using 20 Hz biphasic pulses up to 1100 uA can improve retinal function in human eyes with Central Retinal Artery Occlusion (CRAO) [2]. Most recent experiments report that 5 ms biphasic pulses at 20 Hz produce a tendency for most functional human visual parameters to improve or remain constant such as Visual Acuity (VA), Visual Field (VF), etc. [3]. In experiments with animals, it is present the same tendency to apply squared electrical pulses between 0.5 and 5 ms/phase at 20 Hz, and a range of current intensities from 50 to 500 mA [4]. However, retinal cellular processes do not have sudden transients, as is proposed by the model of photoreceptors ionic currents [5], which have non linear dynamics against time.

The relationship between the parameters of TES and its neuroprotective effect in axotomized retinal ganglion cells (RGCs) is not clear yet. TES generally has been proposed using pulse trains [2-4] to modulate neural activity. However, biphasic waveform does not allow fine control of the pattern of elicited activity. Usui *et al*. [5] reported that a single rod behaves as a bandpass filter whose characteristics are affected by the stimulus strength and frequency, and their network model indicates that the contribution of individual ionic currents to band-pass filtering of small signals is largely regulated by the calcium-dependent currents ***IK*(*Ca*)** and ***ICl*(*Ca*)**, whereas the filtering of large signals is regulated by the hyperpolarization-activated current, ***Ih***. Furthermore, the rod network model electrically interconnects between single

rod models and reveals that the acceleration of signals that spread laterally through the rod network is not attributed to ***Ih*** but ***IK(Ca)*** [5]. The use of alternative stimulus waveforms to improve the control of neural activation has not been well studied. The choice of stimulus waveform for use in TES should be made with some understanding of the temporal response properties of the neurons being activated. The goal is to find the waveform parameters to optimally excite a group of neurons. It is first necessary to find the waveform which these neurons are more sensitive.

The flow of ions through neural membrane cells is analogous to the sum of positive and negative electrical currents at a node; this implies the generation of multiple action potential waveforms. Neuronal graded action potentials play a central role in retinal process between the photoreceptors and the RGCs. In this way retinomorphic waveforms designed for TES should be analogous to biological computation. We suppose that the use of novel stimulus waveforms has the potential to improve control and effect of the patterns of elicit neural activation, both in terms of the temporal structure of elicited spike trains, and in the types of neurons or neuronal substructures being activated.

According to cellular and neural threshold which explains the biochemical communication process by means ionic exchange; electrical, mechanical and chemical impulses can fire this process [6], but in no cases do those processes have a high frequency behavior [5,7]. With this in mind, we have proposed an experimental protocol in order to apply TES to 28 patients with Retinitis Pigmentosa (RP) diagnosis (Dx), along a period of 52 weeks using a stimulation waveform model based on the natural human cellular response to a light impulse, previously modeled and reported [8,9].

1.1. Waveform Mathematical Model

The stimulation waveform reported in this paper and used in experiments (registered at clinicaltrials.gov NCT-00802698) fits more accurately with the human ocular system, because it is a copy of the voltage waveforms present in the cornea. When light stimulated the human retina and registered using a multi-focal electroretinography (mfERG), the curve was processed to obtain a set of mathematical approximation functions [8]; we modeled the curve by means of the mean squared statistical regression method getting the description of the electroretinography (ERG) by a continuous polynomial [9].

The Linear Model

The general model for each curve section is indicated in Equation (1), where ***t*** represents the time, and ***f(t)*** the voltage.

$$f(t) = a_0 t^0 + a_1 t^1 + a_2 t^2 + \cdots + a_n t^n \quad (1)$$

Figure 1(a) shows a common biphasic waveform applied in TES research [2] and **Figure 1(b)** the simulation of the modeled voltage waveform, from a healthy volunteer's mfERG [8].

The proposed polynomial in Equation (1) is linear; however, the mfERG curve has a non linear behavior. To avoid that difficulty, the fitting curve was divided into three sections: we calculated the middle time between a voltage crest and a trough in order to locate the beginning and the end between data groups [10] shown in **Table 1**; the approach is a non linear approximation of the waveform required. **Table 2** shows the linear polynomials to define the mathematical model.

1.2. Adaptive Model

In order to estimate the analog stimulating signal, an adaptive Finite Impulse Response (FIR) filter is then proposed, and its coefficients are estimated from an adaptive identification system in which weights are calculated by the Normalized Least Mean Squared (NLMS) algorithm. The polynomial models are represented in **Figure 2** by $Y(n)$, using 1 ms as sampling time; the constant factor k digitally limits the waveform voltage amplitude [8,9].

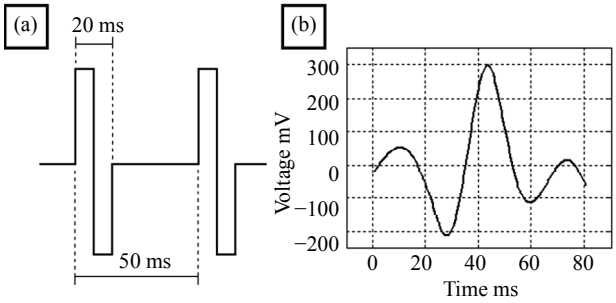

Figure 1. (a) Biphasic waveform applied on transcorneal experiments [2]; (b) Simulation of the voltage waveform used in these experiments [8].

Table 1. Time parameters for each mathematical model.

Time intervals	Section 1	Section 2	Section 3
Start time (ms)	0	39.95	71.73
End time (ms)	36.13	69.56	84.74

Table 2. Mathematical models.

Section	Fitting polynomials (t represents time)
1	$-0.1517 - 0.1683\,t + 0.1234\,t^2 - 0.1798\,t^3 + 0.1293\,t^4$
2	$(1\times10^4)\times(1.1975 - 0.1024\,t + 0.0032\,t^2 - 0.000012\,t^3)$
3	$(1\times10^4)\times(3.0895 - 0.1463\,t + 0.0026\,t^2 - 0.00001346\,t^3)$

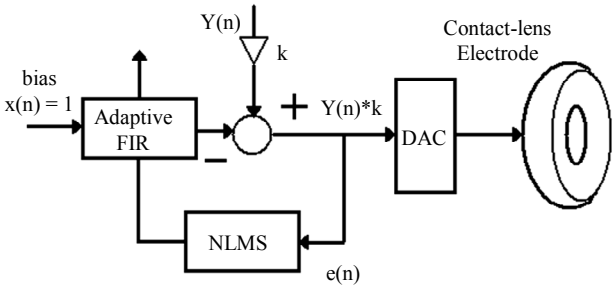

Figure 2. Block diagram of the adaptive system [8,10].

Convergence Algorithm

The system's adaptation is carried out by using the normalized convergence algorithm NLMS, shown in Equation (2), using $\alpha = 1$ and $x(n) = 1$ as a bias constant vector. In order to calculate the adaptive FIR weights $w(n)$; $x^T(n)$ indicates the transpose of the vector $x(n)$.

$$w(n+1) = w(n) + \left[\frac{\alpha}{x(n) * x^T(n)}\right] * x(n) * e(n) \quad (2)$$

1.3. Electronic Design

The FIR filter output is programmed into a microcontroller's memory, allowing us to convert the digital data into an analog signal, indicated in **Figure 2** as digital to analog converter (DAC). Using conventional electronics, we designed a portable electronic device preprogrammed with the electrical phosphene threshold (EPT) average, previously reported [9,10]. Those characteristics permit the transcorneal electrotherapy to be randomized for each patient.

2. SUBJECTS AND METHODS

This research followed the tenets of the Declaration of Helsinki, all patients gave written informed consent after an explanation of the nature and possible consequences of the study; the research protocol was previously approved and registered by the human experimentation institutional committee APEC hospital (registered at clinicaltrials. gov NCT00802698) which was conducted according to good clinical practice (GCP).

The electrodes applied in this research in order to stimulate corneal tissue are shown in **Figure 4(a)**, and they are those commonly used to measure voltage responses in ERG tests: 2 gold-cup scalp for reference and ground electrodes and a monopolar contact-lens electrode, commonly known as the Ganzfeld contact-lens (ERG-jet, Universo Plastique Switzerland), **Figure 4(b)** shows the analog waveform present in the electrodes when the stimulator is active.

Before beginning the patient's stimulation, slit-lamp examinations and ophthalmoscopy were performed, visual acuity (VA) was tested using Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart, Humphrey 24-2 BB visual fields (Humphrey Instruments, San Leandro, CA, USA) and visionmonitor8k electrophysiological recordings (Metrovision, Pérenchies, France) baseline and every 10 weeks. After those examinations, we chose the eye with the worst visual acuity (lower than 20/20) or worst visual capacity (ETDRS characters read) as the eye under test. To assess the changes induced by TES, those examinations and tests were repeated every five weeks for each patient, in order to monitor the TES effect.

2.1. Inclusion Criteria

We selected 28 volunteers suffering from classic RP and/or Usher syndrome type I or II, female (not pregnant women) or male older than 18 years, without macular edema or other related ocular diseases such as glaucoma, nor previous ocular surgery (intraocular lens (IL), retinopexia, vitrectomy, trabeculectomy), and typical intraocular pressure around 14 to 16 mmHg.

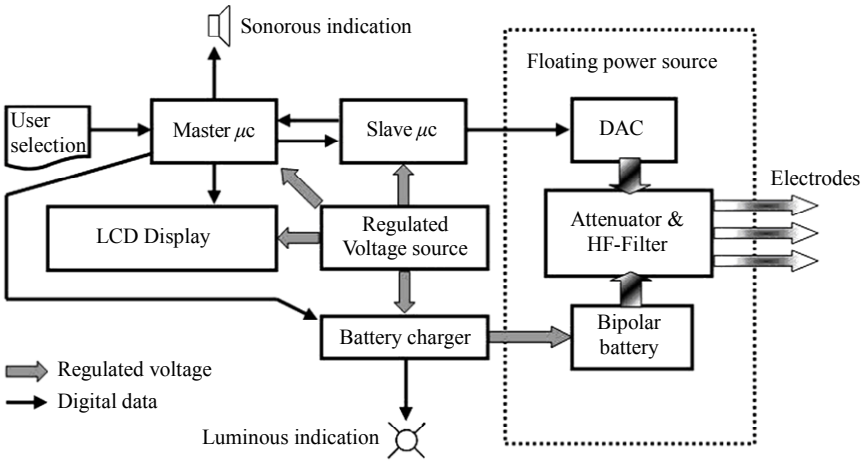

Figure 3. Block diagram of the electronic system [9,10].

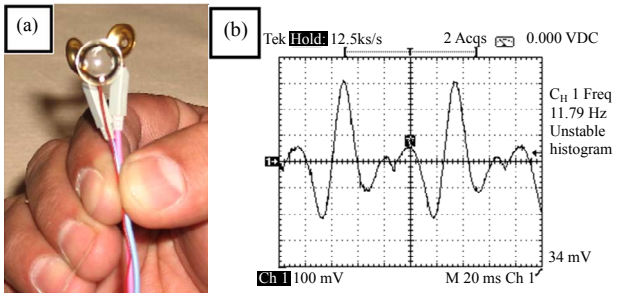

Figure 4. (a) Stimulating electrodes; (b) Voltage waveform measured with osciloscope [9].

2.2. Methods

All patients were transcorneally stimulated 45 minutes per week during fifty two weeks, with the voltage waveform shown in **Figure 4(b)** calibrated with maximum crest to 300 mV, and frequency of 11.8 Hz, which is the analog voltage signal generated by using the bipolar voltage waveform generator shown in **Figure 3**. In order to compare the evolution in the Stimulated Eye (SE), we recorded the visual capacities for the contralateral eye too (Non Stimulated Eye NSE); those were the control parameters.

Electrodes Placement

Patients were prepared with the electrodes, following the standard ERG procedure according to the ISCEV standard [2,8-12], previous to each TES session as is described: the skin of the patient's face was cleaned by applying propanediol 1.2 with sterilized cotton. The ground electrode and the electrical reference electrode were placed by applying polyoxyethylene 20 and attaching them with adhesive tape. A drop of tetracaine hydrochloride 5 mg was applied in the patient's eye to reduce the mild foreign body sensation and the lens electrode was placed on the cornea applying hipromelosa 2% into the lens, this procedure was done only to the eye being tested. **Figure 5** shows the patient wearing the electrodes.

3. RESULTS

This protocol started with 42 patients but only 28 completed the 52 week stimulation period and the last follow-up visit (55th week). There were no adverse events reported (ketaritis, irritation of conjunctiva, etc.), produced by the disposable contact-lens electrode.

3.1. Results of Average VA of All Patients

In order to verify the effect of TES in visual capacities of patients, we used the least mean squared (LMS) lineal regression method, to compare the tendency between ETDRS data, for SE and NSE. **Figure 6** shows the statistical comparison of VA average measurements between SE against NSE for all patients in ETDRS chart Snellen ratio.

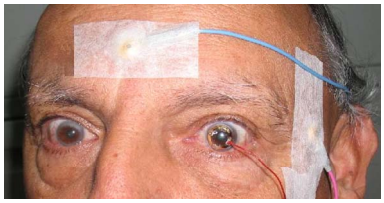

Figure 5. Patient wearing the electrodes ready for TES [9].

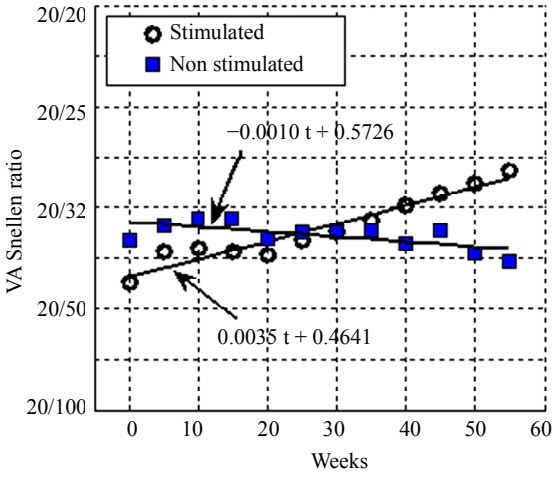

Figure 6. Comparison of the VA average measurements between SE (circle), vs NSE (square) for all patients and the statistical approximation equation (solid line).

As we can see, the average statistical tendency is growth for VA in Snellen ratio for SE and it is represented by the positive slope in the equation (correlation coefficient = 0.9629). On the other hand for NSE the same equation has a negative slope (correlation coefficient = 0.9272), which indicates a constant decrease of the VA average in those results. The VA average for SE reaches similar ETDRS average values around 25 weeks of treatment.

3.2. Results of Average VA of all Patients: Comparison vs Control Parameters

Similar results are presented by read characters in the same ETDRS chart. **Figure 7** shows this comparison.

3.3. Effect of TES Considering the Age of Patients

In order to compare the effect of TES between groups of patients, we analyzed the VA average by categorizing patients in three age groups: subjects younger than 30, between 31 and 50 and older than 51 years old. **Figure 8** shows those results.

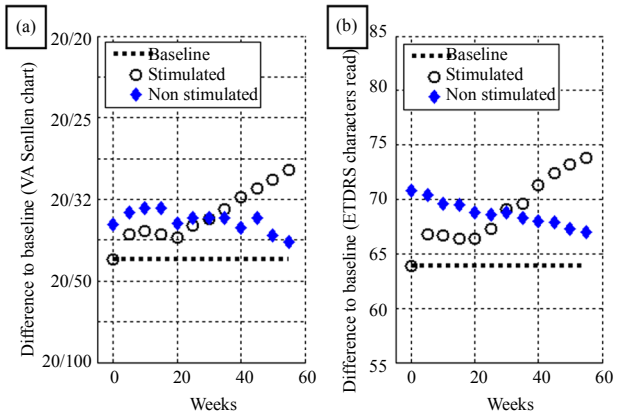

Figure 7. Comparison of lectures between SE (circle), vs NSE (diamond) for all patients: (a) VA average in Snellen ratio; (b) ETDRS average of characters read.

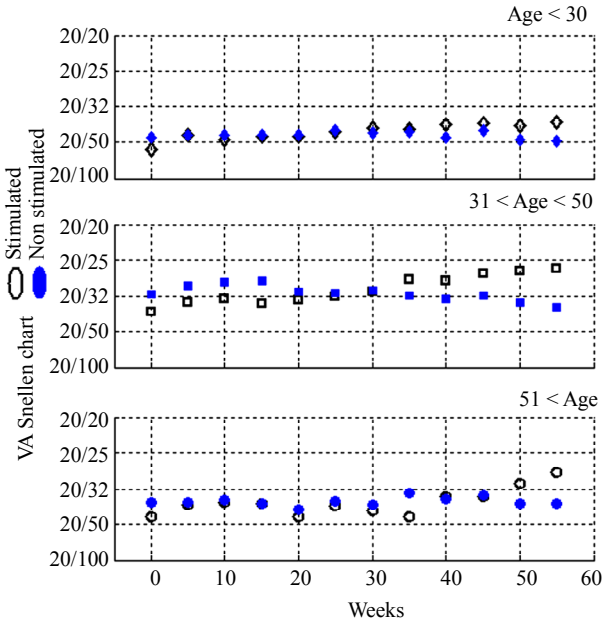

Figure 8. Comparison of the VA average lectures between SE (edge) vs NSE (shaded) for each age group.

In all cases the VA average for SE has a slight tendency to grow but NSE shows a declining behavior throughout the 55 weeks. In cases of patients younger than 30, eyes with lower VA reach the same lecture values than NSE after 20 weeks of treatment, but patients between 31 to 50 years old; the same condition is reached after 30 weeks, in cases of patients older than 51 that condition is reached after the 45th week. In all cases the VA average for SE improves over time.

Table 3 shows statistical data for the linear regression analysis. The first coefficient of SE model is positive (slope), which indicates that the tendency of data is growing with time (t); opposite to the same parameter for NSE, which has negative slope and tendency to decrease versus time. The correlation coefficient (r) is a measurement of the strength of the linear dependence between two variables; a value equal to 1 implies that linear equation describes the relationship between the variables perfectly; a value 0 implies that there is no linear correlation. The coefficient of determination (r^2) which provides a measurement of how well future outcomes are likely to be predicted by the model and standard error (StdError) is the difference between the estimate and the true value.

3.4. Analysis for Time Since Diagnosis

A similar behavior occurred for the time since Dx group: fewer than 5 years, between 5 to 10 years and higher than 10 years from the Dx time. **Figure 9** shows the graphic results, and **Table 4** their statistical model and results.

As we can see the VA average at least remain constant throughout the 55 week period, in the case of the 10 < Dx time group in both SE and NSE, but in cases for Dx time < 5 years and 5 < Dx time < 10 years, the VA for SE is very close to the VA average for NSE around week 25 of treatment, then those values keep on growing, compared with average VA for NSE which decreases with time.

In **Table 4** the linear model for SE is positive in all cases, but for NSE it is negative in two groups, which represents a similar behavior that was described in **Table 3**.

3.5. According to the Genetic Variation

Another group of patients has been established according to the type of diagnosis: classic RP, Usher syndrome I

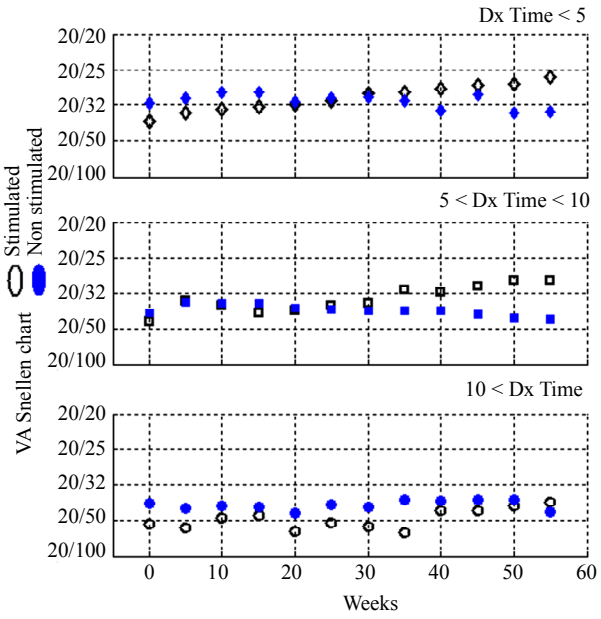

Figure 9. Comparison of the VA average lectures between SE (edge) vs NSE (shaded) for time since diagnosis (years) groups.

Table 3. Linear regression results for VA: *Age of patients* (*years*).

	Group	Regression model	*r*	r^2	*StdError*
Stimulated	age < 30	VA(t) = 0.0023 t + 0.3967	0.8668	0.9310	0.0173
	31 < age < 50	VA(t) = 0.0044 t + 0.5123	0.9431	0.9711	0.0205
	51 < age	VA(t) = 0.0030 t + 0.4416	0.4784	0.6916	0.0586
Non stimulated	age < 30	VA(t) = −0.0002 t + 0.4466	0.0445	0.2109	0.0195
	31 < age < 50	VA(t) = −0.0019 t + 0.6682	0.6119	0.7823	0.0289
	51 < age	VA(t) = 0.0003 t + 0.5177	0.0510	0.2258	0.0251

Table 4. Linear regression results for VA: *Time since diagnosis* (*years*).

	Group	Linear model	*r*	r^2	*StdError*
Stimulated	Time < 5	VA = 0.0042 t + 0.5244	0.9829	0.9914	0.0104
	5 < Time < 10	VA = 0.0037 t + 0.4641	0.7972	0.8929	0.0351
	10 < Time	VA = 0.0020 t + 0.3536	0.4027	0.6346	0.0459
Non stimulated	Time < 5	VA = −0.0013 t + 0.6565	0.3368	0.5804	0.0342
	5 < Time < 10	VA = −0.0013 t + 0.5403	0.5773	0.7598	0.0210
	10 < Time	VA = 0.0003 t + 0.4782	0.0437	0.2091	0.0251

and Usher syndrome II, **Figure 10** shows their characteristics.

These results are similar to those reported in **Tables 3** and **4**, for SE patients the slope in their linear model is positive, but negative for NSE (in all cases) which indicates the tendency to rise and drop respectively against time of VA in both analyses. **Table 5** shows the regression analysis parameter for this group of patients.

The 82.14% of the cases (23/28 patients) were unable to finish at least one of the Humphrey 24-2 BB visual fields test, due to the device automated fixation control (AFC), those patients could not focus their eye on the monitor's central point through out the test, for several trials.

Those data did not reach statistical significance. In cases of a-wave, b-wave and implicit time for ERG recordings. The 67.85% of stimulated patient's eye did not complete at least one test, again due to the AFC when the visionmonitor8k system was used; those data were not considered for statistical analysis.

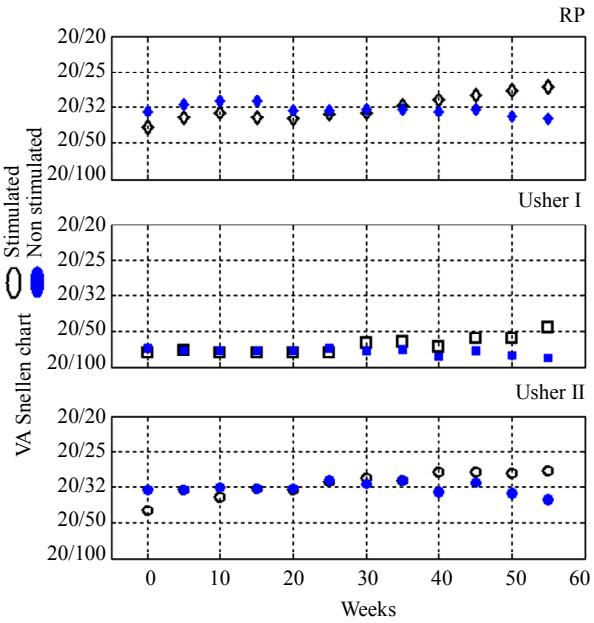

Figure 10. Comparison of the VA average lectures between SE (edge) vs NSE (shaded) accords the type of diagnosis.

4. DISCUSSION

Statistical analyses indicate that TES applied to patients suffering RP, Usher syndrome I and/or II, in general improves their VA 48.15% (without separate patients in groups), meanwhile NSE has a general decreasing tendency around −8.06% in respect to the basal VA average measurements. The average amount of ETDRS characters read had similar changes too; for SE the average difference is 15.6% but for NSE the same difference is −5.45% throughout the 55 weeks (graphical data shown in **Figure 7(b)**).

Statistically the group composed of SE of patients with less than 5 years since diagnosis is the most effi-

Table 5. Linear regression results for VA: *Diagnosis type.*

	Group	Linear model	r	r^2	*StdError*
Stimulated	RP	VA = 0.0038 t + 0.4919	0.8915	0.9442	0.0251
	Usher I	VA = 0.0022 t + 0.2550	0.7602	0.8719	0.0236
	Usher II	VA = 0.0034 t + 0.5257	0.8384	0.9156	0.0281
Non stimulated	RP	VA = −0.0012 t + 0.6205	0.4674	0.6837	0.0233
	Usher I	VA = −0.0007 t + 0.3045	0.5167	0.7188	0.0134
	Usher II	VA = −0.0004 t + 0.6053	0.0471	0.2170	0.0331

cient modeled, because their correlation coefficient (r) and coefficient of determination (r^2) are so close to 1 (**Table 4**), followed by the group of SE of patients between 31 and 50 years old, with the same characteristics (**Table 3**). This means that the variability of measurements (VA) is low enough to describe the statistical modeled tendency, making the model accurate for statistical validation.

With those estimations it is possible to affirm the safety of the proposed TES waveform and parameters as well as a partial effect of recovery and in some cases the improvement of VA characteristics. It is more challenging to prove the efficacy of treatment and establish methods of comparison between similar treatments [3] in a disease such as RP, due to the natural course of disease progression in these patients, it can be highly variable [3]. We acknowledge that our trial is small and most results are not statistically significant, but in further proposed protocols we will consider correcting the statistical validation.

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