



REVIEW

Electrical Stimulation as a Means for Improving Vision



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Evolving research has provided evidence that noninvasive electrical stimulation (ES) of the eye may be a promising therapy for either preserving or restoring vision in several retinal and optic nerve diseases. In this review, we focus on minimally invasive strategies for the delivery of ES and accordingly summarize the current literature on transcorneal, transorbital, and transpalpebral ES in both animal experiments and clinical studies. Various mechanisms are believed to underlie the effects of ES, including increased production of neurotrophic agents, improved chorioretinal blood circulation, and inhibition of proinflammatory cytokines. Different animal models have demonstrated favorable effects of ES on both the retina and the optic nerve. Promising effects of ES have also been demonstrated in clinical studies; however, all current studies have a lack of randomization and/or a control group (sham). There is thus a pressing need for a deeper understanding of the underlying mechanisms that govern clinical success and optimization of stimulation parameters in animal studies. In addition, such research should be followed by large, prospective, clinical studies to explore the full potential of ES. Through this review, we aim to provide insight to guide future research on ES as a potential therapy for improving vision. (*Am J Pathol* 2016, 186: 2783–2797; <http://dx.doi.org/10.1016/j.ajpath.2016.07.017>)

Eye Diseases and Treatment Options

Blindness affects 39 million people worldwide, and its prevalence continuously increases with an aging population (<http://www.who.int/mediacentre/factsheets/fs282/en>). The leading causes of irreversible blindness in the developed world include glaucoma, age-related macular degeneration (AMD), diabetic retinopathy, and retinitis pigmentosa (RP). Glaucoma refers to a group of ocular diseases that result in damage to the optic nerve, leading to progressive, irreversible loss of retinal ganglion cells,¹ and it is the second leading cause of blindness worldwide.² It is estimated that by 2020, approximately 11 million individuals will be blind from glaucoma.² Current glaucoma therapies, including medication, laser trabeculoplasty, surgery, or a combination of any of these, are directed solely at lowering intraocular pressure, which slows vision loss for some patients but

cannot restore vision loss due to disease. AMD is another progressive disease leading to blindness as a result of photoreceptor cell loss in the macula (ie, the central part of the retina). It primarily affects central vision, which is critical for daily activities, such as reading and driving. AMD is the third leading cause of blindness in the world and the primary cause of visual deficiency in industrialized countries.³ Clinically, AMD is divided into two forms: wet and dry. There are currently several treatment options for wet AMD. However, no established therapy is available for dry

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AMD, which constitutes 85% to 90% of known cases. Certain treatments, including intravitreal injection of anti-vascular endothelial growth factor, have shown considerable success in slowing disease progression and reducing the number of blind people worldwide by preventing further neovascularization from wet AMD. However, no well-documented cures exist that can reverse damage that has already been inflicted to the photoreceptors. RP encompasses several genetic defects that result in photoreceptor loss and blindness. The prevalence of RP is reported to be 1:3000 to 1:5000.⁴ In contrast to AMD, the retina is first affected peripherally, with gradual progression to the central retina. RP targets rod photoreceptors, thus initially causing poor peripheral and night vision.

Although there are no currently available cures for these potentially blinding conditions (eg, glaucoma, RP, and AMD), there are many fields of research that give hope of visual restoration to patients with end-stage eye disease. Visual cycle modulators that mediate the intracellular processing of vitamin A are currently being applied in clinical trials for RP, and initial evidence has shown that they slow progression of disease and may provide better vision in patients with mild-to-moderate disease.⁵ Gene therapy aims at treating, curing, or preventing disease by delivering genes into the eyes; however, current therapies are primarily experimental, with most human clinical trials still in the research phase.⁶ For patients only retaining light perception, optogenetic (ie, the use of genetic methods combined with optical technology to achieve retinal neuron function) and stem cell therapies are promising strategies for improving or restoring vision.⁷

ES in Ophthalmology

The first-reported electrical stimulation (ES) of the eye to generate visual sensations to light was performed in 1755 by Charles LeRoy, who applied an electrical discharge on the eye surface of a patient blind from cataracts. The patient reported that the ES provoked strong flashes of light or phosphene. In 1873, Henri Dor reported the beneficial effects of ES on the eye via treatment of amblyopia, amauroses, glaucoma, retinoblastoma, and white optic atrophy.⁸ In 1929, Otfried Foerster, a German neurosurgeon, reported a neural response to ES in a patient's visual cortex.⁹ In 1974, the ES of the visual system was shown to elicit visual perceptions using suprathreshold stimulation.¹⁰ Thirty years later, the therapeutic potential of subthreshold ES of the retina was identified by Chow et al.¹¹ The authors showed that patients having inactive subretinal chips generating only subthreshold currents exhibited visual improvement in areas far from the site of the electrical device, suggesting a generalized neuroprotective effect of ES. This finding was associated with the expression of neurotrophic factors and sparked a research interest in the effects of ES in animal experiments and thereafter in clinical studies for treating blindness.

ES: Methods of Delivery

During the past 10 years, there has been a significant increase in research on developing an ES treatment for various eye diseases. The basis of the therapeutic strategy is to stimulate neurons along the visual pathway with electrical current. Presently, there are eight routes by which ES has been delivered to patients with the purpose of improving vision: transpalpebral, transorbital, transcorneal, subretinal, epiretinal, and transchoroidal approaches, as well as the direct stimulation of the optic nerve or brain (Figure 1). Ocular stimulation targets the remaining retinal cells, whereas stimulation of the brain targets the higher visual structures. Although ocular stimulations are minimally invasive and simple to implement, stimulation of the brain is useful when connections between the eye and brain are affected, such as in advanced glaucoma.

Retinal Prostheses

Retinal prostheses (alias retinal implants or chips) use energy converters to generate electricity to mimic photoreceptor activities. Epiretinal implants electrically target the ganglion cell layer, subretinal implants primarily target the inner nuclear layer of the retina, and transchoroidal implants stimulate the retina from the outer region.¹² Patients with RP usually exhibit defective pigment epithelium and photoreceptors, but the inner retina and ganglion cell layer are intact. To restore visual function, retinal prostheses must detect light, converting light energy into electricity and thereby activating downstream retinal neurons. The field of visual prosthetics has progressed significantly since the first implantation in the 1960s¹³; however, many challenges must still be overcome before it can effectively restore vision in blind patients.¹²

Minimally Invasive ES

Transpalpebral, transorbital, and transcorneal ES (TES) have the advantage of being minimally invasive, only touching the skin and the cornea, with minor adverse effects reported. The use of these approaches reduces the risk of severe complications compared to retinal prostheses. It is of utmost importance that ES is minimally invasive; therefore, the choice of electrodes must be taken into consideration. In both animal experiments and clinical studies, TES has been widely adapted, and the contact lens electrodes are most commonly used. Until now, three types of electrodes have been used in TES: Dawson-Trick-Litzkow (DTL)-Plus electrodes, electroretinography (ERG)-Jet electrodes, and golden ring electrodes, the last lacking a contact lens. DTL-Plus and ERG-Jet electrodes have been used in clinical studies and only negligibly stimulated different areas of the retina. In animal experiments, the ERG-Jet electrode is mostly used because of the simplicity of the procedure for fastening the electrodes onto animals. Transpalpebral

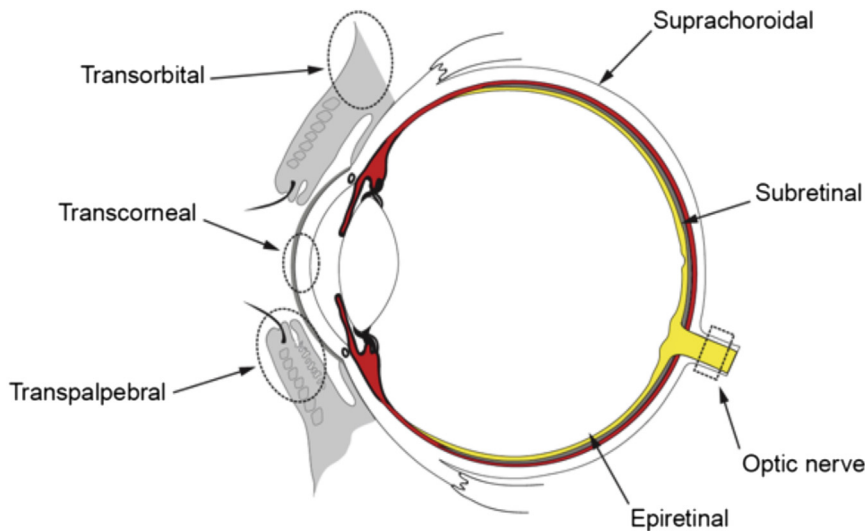


Figure 1 Different routes of electrical stimulation of the eye. The **red circle** represents choroid, except for the anterior part of the eye. The **gray semicircle** represents the retinal pigment epithelial cells, and the **yellow semicircle** illustrates the retina. Image is courtesy of Håkon Raanes (Norway).

(electrodes placed on the eyelids) and transorbital (electrodes placed at or near the eyeball) ES are other minimally invasive procedures. In the present review, we will systematically discuss the experimental populations and parameters, evaluation methods, major findings, advances, and challenges of the various ES procedures.

Animal Experiments

Many research groups have shown favorable effects of ES on the retina and optic nerve using rats, cats, and rabbits as experimental animals. So far, there are no animal studies on transpalpebral ES. However, beneficial effects of ES have been shown in one study using transorbital ES¹⁴ and in several animal experiments using TES (Table 1).^{15–35} These studies can be categorized as follows: i) healthy animals^{17–19,23,26,31,34}; ii) transgenic animals^{22,28}; iii) animals as a disease model for RP²¹; iv) animals with induced ischemic insult,^{27,29,33} optic nerve crush,^{15,16,20,32} and transected optic nerve^{24,25}; and v) animal cells isolated from the retina.³⁵

TES in Animal Models

In 2005, Morimoto et al²⁴ observed that the survival of retinal ganglion cells (RGCs) was preserved from degeneration after transection of the optic nerve in rats, and that the degree of the electric charge was important for the rescue of cells. It was also demonstrated that insulin-like growth factor 1 (IGF-1) in the retina was up-regulated after stimulation. IGF-1 was initially strongly expressed in Müller cells and then also in the inner retina. In another study, the current intensity, frequency, pulse duration, waveform, and number of TES sessions were changed systematically.²⁵ This vigorous approach demonstrated repeated stimulation after optic nerve transection to be the most advantageous. Furthermore, the highest neuroprotective effect on RGCs was

achieved using the following stimulation parameters: 1 and 2 milliseconds per phase, 100 and 200 μ A, frequency of 1.5 and 20 Hz, and at least a 30-minute duration.

Enhanced survival of RGCs has also been observed after optic nerve crush,^{15,16,20,32} after light-induced retinal damage,²⁶ and in ischemic rat retinas.³³ Tagami et al³² revealed that the increased survival of RGCs was in accordance with the number of TES applications and that the daily application of TES exhibited the most effect. Furthermore, daily TES administration resulted in the up-regulated expression of IGF-1 to a greater extent than a single application of TES. Finally, enhanced regeneration of RGC axons by daily application of TES was completely blocked by a specific antagonist to the IGF-1 receptor, whereas the promotion of surviving RGCs was not.³²

In a study involving Royal College of Surgeons rats, a generally used model for inherited retinal degeneration such as RP, the researchers demonstrated that retinal degenerative processes are markedly slowed by TES. TES increased survival of photoreceptors, as suggested by a significantly greater thickness of the outer nuclear layer, preserved ERG b-wave, and impaired retinal function in Royal College of Surgeons rats.²¹ In a study by Schatz et al,³⁶ TES before mild light exposure temporarily preserved b-wave amplitudes and outer segment length, and reduced photoreceptor cell death after 2 weeks. The effects observed in this study were minor compared to the effects reported by Ni et al,²⁶ where TES sessions were repeated and different electrode configurations were used. In a rabbit model of rhodopsin mutations that mimic RP, TES resulted in both increased photoreceptor survival and improved retinal function.²² In P23H transgenic rats, delivery of TES twice per week for 12 weeks resulted in the significant preservation of photoreceptor sensitivity, whereas no histological changes accompanied the stimulation.²⁸ A possible explanation for the unchanged morphology may be the low electrical intensity applied in this study.

TES and Changes in Brain Activity

The beneficial effects of TES are not limited to rescuing neurons in the retina. Recently, Sergeeva et al³¹ successfully generated a new method for TES and flicker light stimulation in freely moving rats as well as a setup to record field potentials from the visual cortex and subcortical structures. A considerable advantage of this novel animal model, compared to what was described in previous studies,^{16,21,24,30} was the possibility to stimulate nonanesthetized rats. Another major advantage of this new animal model was that the rats were freely moving, permitting behavioral testing while simultaneously investigating the electrophysiological effects of stimulation. It was shown that the narcosis strongly influenced brain oscillations and thus may have interfered with TES or its effects on the brain. This was in accordance with a recent study in which TES-induced electroencephalogram after-effects were only achieved while stimulating shallow (late) narcosis but not a deep (early) slow-wave stage.³⁰ The visual responses in the cortex caused by TES were primarily detected in the areas representing the peripheral visual field.¹⁸ In this study, the authors showed that the responses were followed by intensive evoked field potentials. When increasing the pulse width or intensity of TES current, the gradual extension of the responsive regions from the cortical areas to areas representing the central visual field was observed.¹⁸

Transorbital ES in Animal Experiments

Compared to TES, the therapeutic effects and physiological mechanisms of transorbital alternating current stimulation are less well studied and are poorly understood. To our knowledge, there is only one published animal experiment that studied the effect of transorbital alternating current stimulation and characterized the responses in several compartments of the visual system.¹⁴ The findings from this study suggested that early stages of visual processing in generating electrically evoked potentials after transorbital alternating current stimulation were important, further proposing that the coordination of the input from the retina to the tectum and thalamus was an essential, functional mechanism in transorbital alternating current stimulation.¹⁴ These suggestions are in accordance with the results presented by Sergeeva et al,³⁰ demonstrating that the structural integrity at early stages of visual processing was essential for the after-effects achieved by TES.

Clinical Studies

The Effects of TES in Clinical Studies

There are 12 published clinical studies on the use of TES (Table 2).^{36–47} A controlled, randomized, and partially

masked short-term study included 24 patients with RP and demonstrated significant improvements in visual field area and b-waves of the scotopic ERG.³⁶ The study divided patients into three groups, depending on the strength of stimulation in relation to the individual phosphene threshold (0%, 66%, or 150%). The results showed that all functional parameters were slightly improved or remained constant in the 150% group, whereas there was no marked tendency in the 66% group. Compared to normal subjects, Morimoto et al⁴¹ showed that patients with RP and cone-rod dystrophy demonstrated significantly higher electrical thresholds (ie, T1, threshold current for initial phosphene; T2, threshold for eliciting a phosphene extending into the central field; and P, threshold for a relative pupillary constriction $\geq 3\%$). The authors concluded that TES could be used as one of the most essential tests to select candidates for retinal prostheses. In a study by Inomata et al,³⁹ where three patients with long-standing retinal artery occlusion were treated, TES was found to improve both visual acuity and visual field. Moreover, multifocal ERGs demonstrated that the implicit time and amplitudes of all component waves significantly reformed after the TES treatment, suggesting that TES exhibited favorable effects on both the inner and outer retinal neurons in patients with retinal artery occlusion.

In another study of eight patients with long-standing or fresh branch retinal artery occlusion, improvements of both multifocal ERG and visual field parameters were reported after TES in long-standing cases, although improvements in the visual field were not observed in patients with fresh occlusion.⁴⁴ Naycheva et al⁴³ demonstrated that the slopes of the scotopic a-waves significantly increased in patients with central or branch retinal artery occlusion. TES treatment performed >4 months after the onset of nonarteritic ischemic optic neuropathy exhibited improved visual acuity in two of three eyes examined.³⁸ Although visual acuity became impaired some months after the patients stopped receiving ES, after a second TES treatment, the vision improved again. This finding suggests a causal relationship between the treatment and visual improvement. In a recent study using TES, electrical phosphene threshold varied between disease groups.⁴² Across all tested frequencies (3, 6, 9, 20, 40, and 80 Hz), electrical phosphene thresholds were significantly higher when compared with healthy subjects, except in Stargardt disease patients at 20 Hz. Improvements in visual acuity in a recent case report with best vitelliform macular dystrophy suggest that TES should also be investigated in other cases of retinal dystrophies.⁴⁵ Furthermore, after TES, the phosphene threshold current was markedly higher in patients with retinal degeneration compared with control subjects.⁴⁷

It has been shown that TES (up to 150 μ A, 20 Hz, 30 minutes, one session) increases choroidal blood flow in normally sighted patients, with minimal effects on the general blood circulation and intraocular pressure.⁴⁰ The authors suggested that this is probably an important mechanism that underlies the beneficial effects of TES in

Table 1 TES: Animal Experiments

Reference	Species; disease model	Experimental population; stimulation location	Control group	ES parameters	Evaluation method	Results
Henrich-Noack et al, 2013 ¹⁵	Male hooded rats; induced ONC	16 rats; cornea; one eye	Other eye	100 μ A, 1 millisecond/phase, directly after ONC and on days 3, 7, 11, 15, 19, and 23 after ONC, 30-second duration; delivered at 10, 12, 9, 11, 8, 10, 9, and 12 Hz with 5-second break between each	ICON; ERG recordings	TES inhibits post-traumatic cell death considerably; TES decreases ONC-associated neuronal shrinkage and swelling, exceptionally in long-term surviving RGCs
Henrich-Noack et al, 2013 ¹⁶	Male hooded rats; induced ONC	Eight rats; cornea; both eyes	Eight rats; sham	100 μ A, 20-Hz biphasic square-wave pulses of 1 millisecond/phase, 60-minute duration, stimulated immediately after ONC and on day 11 after induction of ONC	ICON before ONC and on postlesion days 3, 7, and 15; ERG recordings	TES resulted in increased surviving of RGCs; the rate of RGC death was more variable in TES group; changes in morphology of survived neurons were milder in TES group
Kanamoto et al, 2015 ¹⁷	Wistar rats	18 rats; cornea; left eye	Right eye	50/100/200 μ A, 20 Hz, 1-millisecond pulses, 30-minute duration, one session	Enucleated eyes 30 minutes or 24 hours after TES; proteomic analysis of retina	25 Functional proteins exhibited higher levels of expression in TES group compared with control group
Ma et al, 2014 ¹⁸	Healthy adult cats	13 cats; cornea; right eye	—	In optical imaging experiments: 1.2 mA, 5–100 Hz, 2–40-millisecond pulses/phase, 2-second duration; studying effects of different parameters: 0.24–2.64 mA, 20 Hz, 10-millisecond pulse width per phase, 1.2 mA, 20 Hz, 2–22 millisecond pulse width per phase	Multiwavelength optical imaging of intrinsic signals; electrophysiological recordings; hemoglobin oxygenation; cerebral blood volume	OIS activation regions in the visual cortex were correlative with TES; ascending current intensities and longer pulse width increased the extent of activation; largest response observed at 10–20 Hz; TES led to activation of peripheral retina
Mihashi et al, 2011 ¹⁹	Healthy adult cats	Two cats; cornea; both eyes	—	Maximum current up to 1 mA, 20 Hz, 20 paired biphasic pulses of 5 milliseconds	Electrophysiological recordings; fundus images	TES activates the RGCs; TES changes the blood flow
Miyake et al, 2007 ²⁰	Long-Evans rats; induced ONC	Five rats; cornea	Five rats; sham	500 μ A, 20 Hz, pulses, 50-microsecond duration; started immediately after the ONC, applied for 6 hours	VEP; histology	TES instantly increased VEP amplitude, which was weakened by the ONC; increased number of axons in retina observed centrally beyond the crushed region when compared with the control group
Morimoto et al, 2007 ²¹	RCS rats; model for RP	18 rats; cornea; left eye	Right eye	50 or 100 μ A, 20 Hz, 1 millisecond, 1-hour duration, one session	ERG recordings; histology	Compared to sham, 100 μ A TES increased the thickness of the ONL at each time point; TES resulted in increased number of surviving photoreceptors and inhibited functional reduction of retina
Morimoto et al, 2012 ²²	Rhodopsin P347L transgenic rabbits	Six rabbits; cornea; left eye	Right eye	700 μ A, 20 Hz, 10 milliseconds/phase, 1-hour duration, once a week for 6 weeks	ERG recordings; histology; immunohistochemistry	TES led to increased survival of photoreceptors and preserved ERGs
Morimoto et al, 2014 ²³	Healthy adult cats	Eight cats; cornea; left eye	—	Biphasic pulses: 0.1, 0.5, 1.0, 2.0 mA, 20 Hz at 20 pulses; pulse durations: 0.5, 1.0, 2.0, 3.0, 5.0, 10.0 milliseconds/phase at 20 Hz at 20 pulses; frequencies of 5, 10, 20, 30, 50 Hz at 5	Optical imaging of reflectance changes in retina; electrophysiological recordings from OC	The intensity increased with the frequency, pulse duration, and current intensity; TES resulted in the reflective changes on the optic disk and retinal vessels, and in activation of retinal neurons

(table continues)

Table 1 (continued)

Reference	Species; disease model	Experimental population; stimulation location	Control group	ES parameters	Evaluation method	Results
Morimoto et al, 2005 ²⁴	Adult Wistar rats; transected ON	26 rats; cornea; both eyes	12 Rats; sham	100 μ A, 20 Hz, 3 milliseconds/phase, 1-hour duration, one session	Quantification of RGC density; RT-PCR; Northern blotting; Western blotting; immunohistochemistry	TES increased the number of surviving axotomized RGCs; the electric charge strength had important role for the degree of rescue; IGF-1 was up-regulated in the retina after TES; IGF-1 was first expressed in the Müller cells and then diffused into the inner retinal layer
Morimoto et al, 2010 ²⁵	Wistar rats; transected ON	36 rats; cornea; left eye	12 Rats; sham; right eye	0.5, 1, 2, 3, and 5 milliseconds/phase, with 100 μ A, 20 Hz for 60 minutes; 50, 100, 200, 300, and 500 μ A with 1 millisecond/phase, 20 Hz, 60 minutes; 0.5, 1, 5, 20, 50, and 100 Hz at 100 μ A, 1 millisecond/phase for 60 minutes; 15, 30, and 60 minutes at 100 μ A, 1 millisecond/phase, and 20 Hz; repeated stimulations on days 0, 4, 7, and 10 after the transection were compared with a single stimulation 14 days after transection	Quantification of RGC density with fluorescence microscope	The optimal neuroprotective parameters were 1 and 2 milliseconds/phase, 100 and 200 μ A, frequency of 1, 5, and 20 Hz; >30 minutes of TES was required to achieve a neuroprotective effect; repeated stimulation was more neuroprotective than a single stimulation 14 days after transection
Ni et al, 2009 ²⁶	SD rats	332 rats; cornea; both eyes	Light stimulation	100–500 μ A, 20–100 Hz, 3 milliseconds, 1.5 hours, one session; 200 or 300 μ A, 20 Hz, 3 milliseconds, one session per 3 days for up to 14 days	ERG recordings; histology; immunohistochemistry; RT-PCR; Western blotting	Post-TES exhibited an enhanced and longer-term protective effect than pre-TES; after TES, expression of <i>Bcl-2</i> was up-regulated, <i>Bax</i> was down-regulated, and levels of CNTF and BDNF were up-regulated
Osako et al, 2013 ²⁷	SD rats; induced NAION	19 rats; cornea	14 Rats; sham	100 μ A, 20 Hz, 1 millisecond/phase, 60-minute duration; TES applied 3 hours after the induction of NAION and was later performed on the 1st, 4th, 7th, 14th, and 28th day	OCT measurements; STR; measurements of the number of surviving RGCs	The use of TES resulted in decreased STR amplitude and the number of RGCs in NAION rats
Rahmani et al, 2013 ²⁸	P23H transgenic rats; mimic autosomal dominant RP	Six rats; cornea; left eye	10 Rats, sham, 16 weeks of age	1.5 μ A, 5 Hz, 40–50 k Ω ; TES applied twice per week, 30-minutes sessions, from 4 to 16 weeks of age	ERG recordings; histology	TES led to preservation of b-wave amplitudes and rod sensitivity; no histological changes were associated with TES treatment
Schatz et al, 2012 ²⁹	SD rats; induced NAION	15 rats; cornea; right eye	15 rats; sham; 3 rats for histology	200 μ A, 20 Hz for 1 hour, biphasic stimuli 2 milliseconds/phase (1 millisecond positive, 1 millisecond negative pulse)	ERG recordings; histology; immunohistochemistry; TUNEL assays	TES resulted in lower b-wave; photoreceptor cell death was observed in sham group, primarily in the superior hemiretina; eyes treated with TES exhibited preservation of ONL thickness and resulted in reduced death of photoreceptor cells

(table continues)

Table 1 (continued)

Reference	Species; disease model	Experimental population; stimulation location	Control group	ES parameters	Evaluation method	Results
Sergeeva et al, 2012 ³⁰	Lister hooded rats; chronically lesioned after ONC	10 rats; cornea	10 rats; sham	100 μ A, 1 millisecond/phase, 30-second trains, 10-second breaks between each stimulation; the frequency of 10, 12, 9, 11, 8, 10, 9, and 12 Hz; repeat after 2-minute break	EEG recordings	EEG was not significantly changed in lesioned rats; TES only exhibited the effect by inducing cortical plasticity when the retina can be excited
Sergeeva et al, 2015 ³¹	Lister hooded rats	24 rats; cornea; both eyes	—	300 μ A, biphasic 2-millisecond pulses, 1 per second, 20-minute duration	Exposed to flicker light; VEP and EER in visual cortex and superior colliculus	Physiological responses recorded after TES
Tagami et al, 2009 ³²	Wistar rats; induced ONC	36 rats; cornea; both eyes	12 Rats; sham	100 μ A, 20 Hz, 1 millisecond/phase, 1-hour duration; four protocols: a single application on day 0, two on day 0 and 7; four on day 0, 4, 7, and 10; and daily applications on days 0–12	Quantification of axonal growth and RGC density; IGF-1 immunostaining of retina	Daily applied TES encourages both survival of RGCs and regeneration of axons after the crush of ON; TES resulted in increased IGF-1 immunoreactivity
Wang et al, 2011 ³³	SD rats; ischemic insult	28 rats; cornea; both eyes	Sham	300 μ A, 20 Hz, 3 milliseconds/phase, 1 hour every 2 days up to 14 days	ERG recordings; histology; confocal laser microscope; Western blotting; immunohistochemistry	Higher density of RGCs in TES treated retinas on day 7 and 14 after ischemia; TES greatly preserved the thickness of separate retinal layers
Willmann et al, 2011 ³⁴	Wild-type brown Norway rats	17 rats; cornea; right eye	16 rats; sham	200 μ A, 20 Hz, 1 millisecond/phase, 1-hour duration, one session	Microarray analysis; RT-PCR; histology; morphometric analysis; ERG recordings	490 Genes exhibited different expression after TES; neuroprotective genes such as <i>Bax</i> or TNF family members were up-regulated; ERG recordings demonstrated physiological retinal function after TES
Zhou et al, 2012 ³⁵	Rat cells	Primary microglia and Müller cells from retinas of SD rat cell line 661W	—	300, 500, 1000, 1600 μ A, 20 Hz, 3 milliseconds, 1 hour, one session	LDH assays; TUNEL assays; immunocytochemistry; RT-PCR; Western blotting	TES led to inhibition of the secretion of IL-1 β and TNF- α in microglia, and to increased secretion of BDNF and CNTF in Müller cells; the death rate was reduced by addition of antibodies to IL-1 β and TNF- α

Bcl-2, B-cell lymphoma-2; BDNF, brain-derived neurotrophic factor; CNTF, ciliary neurotrophic factor; EEG, electroencephalogram; EER, electrically evoked response; ERG, electroretinogram; ES, electrical stimulation; ICON, *in vivo* confocal neuroimaging; IGF-1, insulin growth factor-1; LDH, lactate dehydrogenase; NAION, nonarteritic ischemic optic neuropathy; OC, optic chiasma; OCT, optical coherence tomography; OIS, optical imaging of intrinsic signals; ON, optic nerve; ONC, optic nerve crush; ONL, outer nuclear layer; RCS, Royal College of Surgeons; RGCs, retinal ganglion cells; RP, retinitis pigmentosa; SD, Sprague-Dawley; STR, scotopic threshold response; TES, transcorneal electrical stimulation; VEP, visual evoked potentials; —, not reported.

ischemic retinal diseases. Another study demonstrated that TES at a frequency of 20 Hz evoked pupillary reflexes in subjects with normal vision, whereas biphasic pulse trains at a duration of 0.5 to 1.0 milliseconds and 20- to 50-Hz frequencies evoked phosphene.³⁷ Accordingly, both DTL-Plus and ERG-Jet electrodes showed visual cortex activation in association with the reported phosphene.⁴⁶

Transorbital and Transpalpebral ES in Clinical Trials

There are six published studies on the use of transorbital ES (Table 3)^{48–53} and three on the use of transpalpebral ES

(Table 3).^{54–56} In seven patients with chronic prechiasmatic visual system damage, it was found that transorbital ES strengthened α band functional connectivity, which was associated with perceptual improvements. Therefore, it is speculated that vision loss in the blind is caused not only by primary tissue damage but also by breakdown of synchronization in brain networks.⁴⁸ In addition, transorbital ES in patients with optic nerve damage showed significant increases in detection ability, visual field, and visual acuity.^{49–52} All three published studies on the use of transpalpebral ES were performed in patients with AMD (Table 3).^{54–56} Transpalpebral ES was found to be safe in

Table 2 TES: Clinical Studies

Reference	Disease	Experimental population; stimulation location	Control group	ES parameters	Evaluation method	Results
Schatz et al, 2011 ³⁶	RP	24 patients; cornea; both eyes	Sham	Intensity 66% and 150% of EPT, 20 Hz, 5-millisecond biphasic pulses, 30 minutes per week, for 6 weeks	VA; VF; ERG recordings; color discrimination; EPTs; blood tests	TES improved VF; all functional parameters were improved or remained constant in 150% group; TES led to decreased desaturated color discrimination and VF mean sensitivity; no marked tendency was observed in 66% group
Fujikado et al, 2007 ³⁷	Normal-sighted	Eight patients	—	25–250 μ A, biphasic pulses at 5–50 Hz, 20 pulses of 10-millisecond duration	Measurement of PR	TES with a frequency of 20 Hz yielded the maximum PR; biphasic pulses with duration of 0.5–1.0 millisecond and a frequency of 20–50 Hz were highly efficient for evoking phosphene
Fujikado et al, 2006 ³⁸	NAION; TON	Eight patients; NAION ($n = 3$); TON ($n = 5$); cornea; one eye	Fellow eyes	300–800 μ A, 20 Hz, 10 milliseconds, 30 minutes, one session	EEPR; BCVA; VF	The VA increased in two subjects with NAION and in four subjects with TON
Inomata et al, 2007 ³⁹	RAO	Three patients, two with central and one with branch RAO, cornea; one eye	Fellow eyes	0–1100 μ A until evoking phosphene, 20 Hz, 30-minute duration, once per month for up to 3 months	VA; VF; mfERGs	Improved function of retina in eyes with long-standing RAOs; the VA and mfERGs improved in two cases, and VF was improved in all three cases
Kurimoto et al, 2010 ⁴⁰	Normal-sighted	10 patients; cornea; both eyes	Fellow eyes; sham	Up to 150 μ A, 20 Hz, 30 minutes, one session	LSFG; SBR; IOP; measurement of blood pressure and pulse rate	Increased the chorioretinal blood flow in normal patients with mild effects on the systemic blood circulation and IOP
Morimoto et al, 2006 ⁴¹	RP; CRD	20 patients; RP ($n = 16$); CRD ($n = 4$); cornea	Eight healthy patients	50 μ A–2 mA, biphasic pulses at 20 Hz, 20 pulses of 10-millisecond duration; three electrical current thresholds: T1, T2, and P	EEPR; BCVA; VF; phosphene thresholds	All thresholds significantly higher in patients compared to healthy subjects; T1 and T2 were not correlated with VA, but related to the area and location of the remaining VF; T1 and T2 in RP eyes with EEPR was lower compared to RP eyes without an EEPR
Naycheva et al, 2012 ⁴²	RP; STG; RAO; NAION; POAG	RP ($n = 30$); STG ($n = 14$); RAO ($n = 20$); NAION ($n = 16$); POAG ($n = 17$); cornea	20 Healthy patients	1 μ A–10 mA, 3, 6, 9, 20, 40, and 80 Hz with 10-millisecond biphasic current pulses; 5 millisecond positive, thereafter 5 millisecond negative; periodically switching of the light, every 60–90 seconds	VA; VF; electrophysiology; slit-lamp biomicroscopy; fundus examination; tonometry	EPTs differed between the disease groups; in all groups, EPTs were lowest at 20 Hz; subjects with retinal diseases and across all frequencies exhibited higher EPTs than healthy patients, except in STG at 20 Hz
Naycheva et al, 2013 ⁴³	Central and branch RAO	13 patients; 12 with central, 1 with branch RAO	Three patients; sham	5-milliseconds positive, thereafter 5-milliseconds negative biphasic pulses at 20 Hz, 30 minutes once a week for 6 days, intensity 66% and 150% of EPT	Kinetic and static VFs; VA; full-field and mfERG	The scotopic a-wave slopes increased in 150% treatment group; other parameters in all other groups were unchanged
Oono et al, 2011 ⁴⁴	Branch RAO	Five patients; two fresh and three long-standing cases; cornea; both eyes	—	500–900- μ A, biphasic pulses at 20 Hz, duration 30 minutes	BCVA; mfERGs; automated static perimetry with HFA	TES reforms the visual function in patients with branch RAO, primarily in long-standing cases

(table continues)

Table 2 (continued)

Reference	Disease	Experimental population; stimulation location	Control group	ES parameters	Evaluation method	Results
Ozeki et al, 2013 ⁴⁵	BVMD	One patient; cornea; right eye	—	First treatment: 250 μ A/170 μ A, 20 Hz, 10 milliseconds/phase, 30-minute duration, two sessions with interval of 1 month; second treatment 2 years later: 160 μ A, 20 Hz, 10 milliseconds, 30-minute duration, two sessions with interval of 1 month	BCVA; VF; mfERG	BCVA improved from 20/40–20/30 after 1 month, and from 20/40–20/25 after 6 months; slight improvements for VFs and mfERGs; BCVA decreased to 20/70 after 2 years; second treatment: BCVA improved to 20/30 after 1 month; no improvements in VFs and mfERGs
Xie et al, 2011 ⁴⁶	Normal-sighted	Six patients; cornea; right eye	—	DTL-Plus corneal electrode and ERG-Jet contact lens electrode; 1.5 \times EPT current amplitude, 30-minute duration, 2 Hz, 2-millisecond pulse width; after every 5 minutes of continuous TES, stimulation turned off for 30 seconds	PET imaging; FDG activity	The results with both corneal electrodes demonstrated activation of areas in visual cortex that were related to the reported phosphene percept; ERG-Jet was able to generate brighter phosphene percept compared to DTL-Plus; the use of ERG-Jet led to activation of retinotopically mapped primary visual cortex
Xie et al, 2012 ⁴⁷	RD	Five patients; cornea; right eye	Five healthy patients	First, 30 minutes dark adaptation; 1.5 \times EPT current amplitude, 2-millisecond pulses, 2 Hz with interpulse of 996 milliseconds, 30-minute duration; after every 5 minutes of continuous TES, stimulation turned off for 30 seconds	PET imaging; FDG activity	EPT current was higher in RD patients compared with control; in both groups, TES and light stimulation resulted in activation of retinotopically mapped primary visual cortex

BCVA, best-corrected visual acuity; BVMD, best vitelliform macular dystrophy; CRD, cone-rod dystrophy; DTL, Dawson-Trick-Litzkow; EEP, electrically evoked pupillary response; EPT, electrical phosphene threshold; ERG, electroretinogram; ES, electrical stimulation; FDG, ¹⁸F-fluorodeoxyglucose; HFA, Humphrey field analyzer; IOP, intraocular pressure; LSFG, laser speckle flowgraphy; mfERG, multifocal electroretinogram; NAION, nonarteritic ischemic optic neuropathy; PET, positron emission tomography; POAG, primary open-angle glaucoma; PR, pupillary reflex; RAO, retinal artery occlusion, RD, retinal degeneration; RP, retinitis pigmentosa; SBR, square blur rate; STG, Stargardt disease; TES, transcorneal electrical stimulation; TON, traumatic optic neuropathy; VA, visual acuity; VF, visual field; —, not reported.

patients, and the results demonstrated a provisional increase in visual function in some patients⁵⁴; best-corrected visual acuity was found to be improved in patients with both wet and dry AMD.⁵⁶

Possible Mechanisms Underlying the Effects of ES

Despite several studies showing promising results in both animal experiments and clinical studies, there are presently few reports on the mechanisms of action for ES, making this field still poorly understood. Today, we know that after injuries like optic nerve transection, directly injured RGCs are rapidly lost, and so far there are no treatments that can prevent this process. However, the secondary loss of RGCs whose axons were not directly damaged is considerable,⁵⁷

and the neuroprotective effect of ES is significant in preventing this secondary apoptosis.

The suggested mechanisms that are believed to underlie the effects of TES are summarized and presented in Figure 2. As in other tissues, it is believed that TES increases the expression of neurotrophic factors. It has been suggested that TES increases the number of surviving RGCs *in vivo*, probably because of increased levels of IGF-1 produced by Müller cells.^{24,58} Another study demonstrated that the expression of mRNA encoding brain-derived neurotrophic factor increased and that intracellular protein levels were found in cultured Müller cells after TES,⁵⁹ supported by Ni et al.²⁶ The last study also demonstrated that the levels of ciliary nerve trophic factor and expression of *Bcl-2* were both increased after TES.²⁶ In cultured retinal Müller cells, Sato et al⁶⁰ showed that TES also increased the expression of fibroblast growth factor 2, which was also

Table 3 Transorbital and Transpalpebral ES: Clinical Studies

Reference	Disease	Experimental population; stimulation location	Control group	ES parameters	Evaluation method	Results
Bola et al, 2014 ⁴⁸	Chronic prechiasmatic visual system damage	Seven patients; skin near the eyeball	Eight patients; sham	Current strength above (125%) phosphene thresholds as reported by the patients; applies for 10 days, 40 minutes each	EEG recording	ES strengthened α band functional connectivity, which was associated with perceptual improvements
Fedorov et al, 2011 ⁴⁹	OND	446 patients; upper eye lid	—	Intensity increase stepwise by 10 μ A per second, 5 Hz, two to nine pulses; each daily session of 200–250 cycles with five to seven 1-minute breaks, session length 25–40 minutes; 10-day treatment	EEG recording, VF, VA	ES improved VF size in both eyes; VA was significantly increased in both eyes; increased α and θ power in patients who had VF enlargements but no VA change; nonresponders exhibited increased Δ power spectra in occipital and frontal areas
Gall et al, 2010 ⁵⁰	OND	One patient; skin of the eye lids; both eyes	—	The amplitude was always <600 μ A, 10–30 Hz, 10–15 pulses, single duration of 8.7 \pm 0.8 milliseconds, 30–40-minute duration, daily for 10 days; intensity increase stepwise by 10 μ A per second	VA; VF; static and kinetic perimetry	Detection ability increased; mean perimetric threshold increased
Gall et al, 2011 ⁵¹	OND	24 patients; near the eyeball; both eyes	18 Patients; sham	Intensity increase stepwise by 10 μ A per second, 5 Hz, pulse shape was either square or sinus, two to nine pulses; each session of 200–250 cycles with five to seven 1-minute breaks; 10-day treatment	VF diagnostics with HRP; VA and contrast vision	Detection ability was significantly larger; static and kinetic perimetry provided ES efficacy
Sabel et al, 2011 ⁵²	OND	12 patients; near the eyeball	10 Patients; sham	The amplitude of pulses was <1000 μ A; current intensity increased stepwise by 10 μ A per second; two to nine pulses	HRP; VA; EEG recording	Stimulation resulted in improvement of a VF by 69%; increased temporal procession of visual stimuli
Schmidt et al, 2013 ⁵³	Prechiasmatic partial OND	18 patients; orbital; both eyes	Six patients; sham	Maximal amplitude <500 μ A, 9–37 Hz, two to nine pulses, 10 consecutive days	EEG recording; VF	Enhancement of α activity after ES; the residual VF was significantly improved

(table continues)

Table 3 (continued)

Reference	Disease	Experimental population; stimulation location	Control group	ES parameters	Evaluation method	Results
Anastassiou et al, 2013 ⁵⁴	Dry AMD	12 patients; palpebral; both eyes	10 Patients; sham	150–220 μ A, 5–80 Hz; 5 consecutive days, two sessions on each day, every session eight spots (40 seconds/spot)	VA testing before treatment, after 5 days, after 4 weeks, after 6 months; macular sensitivity and fixation stability with microperimetry; OCT	Stimulation resulted in improved VA in 7 of 12 patients, with more than five letters; contrast sensitivity showed a similar pattern
Chaikin et al, 2015 ⁵⁵	Wet and dry AMD	17 patients; 25 eyes with dry type and 6 eyes with wet type	—	150 μ A; 3–162 Hz; 35-minute session once a week; average number of treatments was 4.8	IO pressure measurements; OCT; VA	Significant improvements in VA in patients with dry type, but not in wet type; in dry-type subjects, 52% of patients exhibited increased VA, and 26% deterioration
Shinoda et al, 2008 ⁵⁶	Wet and dry AMD	21 patients; 16 (27 eyes) with wet type and 5 (7 eyes) with dry type; palpebral; both eyes	—	800 μ A; one 20-minute session was performed four times per day, up to 1 month; 290 Hz for 1 minute, 31 Hz for 2 minutes, 8.9 Hz for 10 minutes, 0.28 Hz for 7 minutes	BCVA before and after 4 weeks; slit-lamp examination; fluorescein angiography; automated static VF testing	All of the patients reported phosphene perception; BCVA improved, but did not reach statistical significance

AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; EEG, electroencephalogram; ES, electrical stimulation; HRP, high-resolution perimetry; IO, intraocular; OND, optic nerve damage; OCT, optical coherence tomography; VA, visual acuity; VF, visual field; —, not reported.

confirmed by Ciavatta et al⁶¹ after implantation of microphotodiode arrays in Royal College of Surgeons rats. It has been suggested that L-type calcium channels probably control the release of these growth factors. This was demonstrated when an L-type voltage-dependent calcium channel blocker (nifedipine) was used to inhibit the up-regulation of IGF-1 and brain-derived neurotrophic factor.^{58,59}

In primary microglia isolated from retinas of Sprague-Dawley rats, the inhibitory effects of ES on the secretion of IL-1 β and tumor necrosis factor- α were confirmed, as well as favorable effects on the production of brain-derived neurotrophic factor and ciliary nerve trophic factor in Müller cells³⁵ and the down-regulation of the proapoptotic gene *Bax*.²⁶ Willmann et al³⁴ also showed that TES led to clear changes in the expression of neuroprotective genes and that different genes may be expressed, depending on whether TES was applied to a healthy or diseased retina. Other effects of ES, investigated using a rat model of retinal ischemia, included increased secretion of glutamine

synthetase from Müller cells, suggested to improve glutamate-mediated neuroexcitotoxicity.³³ Furthermore, ES may also promote neuronal survival by increasing intracellular Ca²⁺ influx, which can cause neuronal cell depolarization and increase intracellular cyclic adenosine monophosphate levels.⁶² TES also was found to improve choroidal blood flow in normal-sighted patients, with mild effects on the systemic blood circulation and intraocular pressure.⁴⁰

The expression of retinal genes and the levels of retinal proteins associated with TES have recently been investigated. Willmann et al³⁴ investigated the effect of TES on mRNA expression, retinal structure, and function. The authors demonstrated that TES induced differential the expression of 490 genes in the retina, including *Bax* and members of the tumor necrosis factor family. Physiological retinal function and intact structural properties were maintained for up to 35 hours after stimulation.³⁴ A proteomic study by Kanamoto et al¹⁷ demonstrated that 25 proteins were up-regulated after TES, including cellular signaling

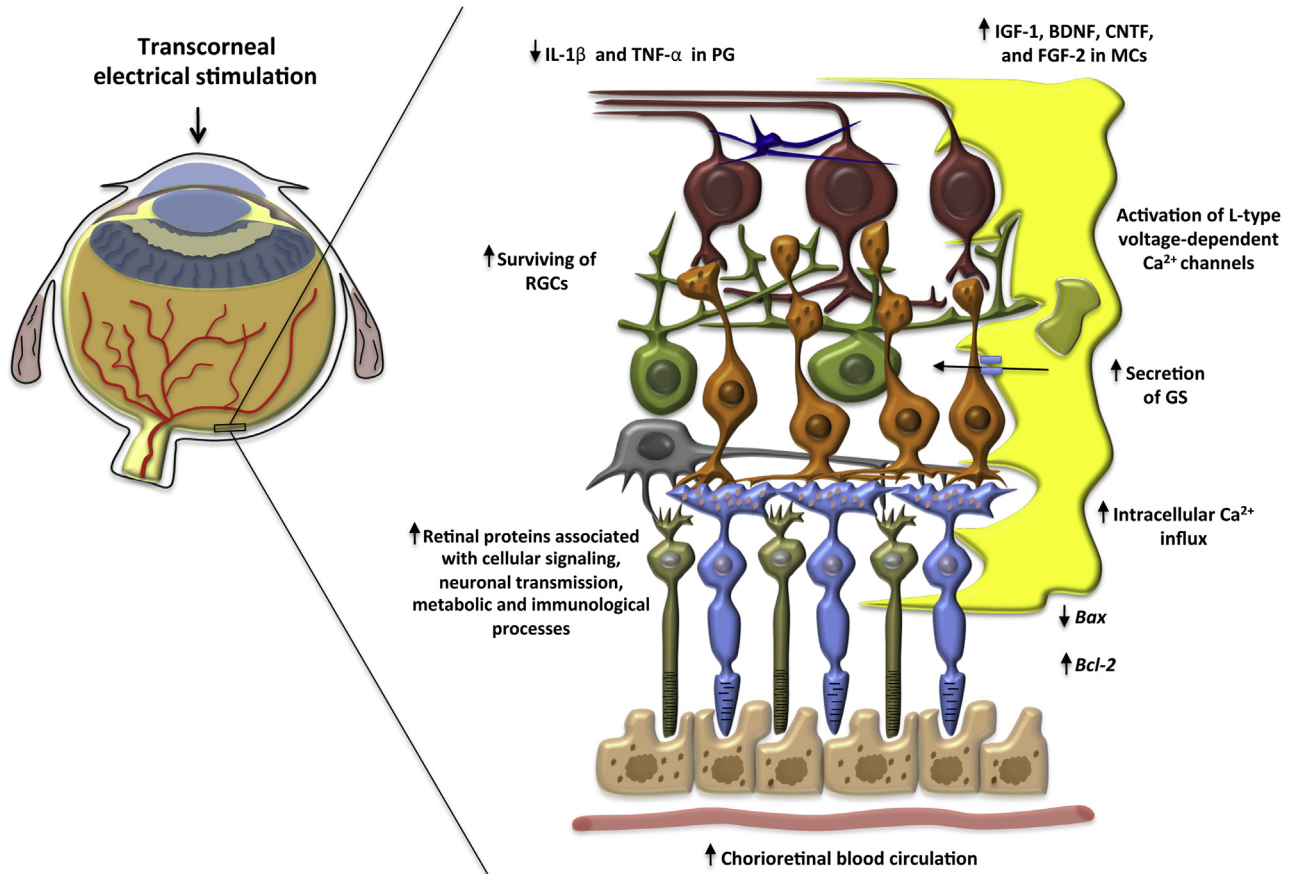


Figure 2 Possible neuroprotective mechanisms underlying the effects of transcorneal electrical stimulation. The cellular structure in the figure represents an enlarged image of the retina. BDNF, brain-derived neurotrophic factor; CNTF, ciliary nerve trophic factor; FGF, fibroblast growth factor; GS, glutamine synthetase; IGF-1, insulin-like growth factor 1; MCs, Müller cells; PG, primary microglia; RGCs, retinal ganglion cells; TNF- α , tumor necrosis factor- α .

proteins, proteins associated with neuronal transmission, metabolic proteins, immunological factors, and structural proteins. The pattern of differentially expressed proteins was altered at 30 minutes and 24 hours after TES, and the authors suggested that TES induced acute and chronic changes in protein expression. It was further proposed that the acute changes were direct and transient effects induced by electric shock to neural cells, whereas the chronic changes were indirect and secondary effects in mRNA expression or protein signaling pathways.¹⁷

Complications and Safety Profile

There are >120 articles on the use of invasive retinal prostheses for ES, making these approaches substantially more studied than other recently described, less invasive techniques. Both transpalpebral and transorbital approaches have the advantage of being minimally invasive (only touching the skin), with minor adverse effects reported. In a clinical study, it was reported that 1 of 21 patients developed contact dermatitis after transpalpebral ES.⁵⁶ One investigation reported light frontal headache

after transorbital ES in 3 of 18 patients.⁵³ Furthermore, among 12 patients studied, 5 had some sensations while under the stimulation electrodes and 1 had spontaneous phosphene.⁵² TES touches only the cornea, which substantially reduces the risk of severe complications compared to retinal implants. The adverse effects were infrequent and mild for both DTL-Plus and ERG-Jet electrodes, with few patients reporting either foreign-body sensations with the DTL-Plus electrode³⁶ or mild transient corneal punctate keratopathy on slit-lamp examination after the use of the ERG-Jet electrode.³⁸ Schatz et al³⁶ also reported minor conjunctiva irritation after intraocular pressure measurements. Other clinical TES studies reported slight corneal superficial punctuate keratopathy,⁴¹ transient superficial keratitis,³⁹ and foreign-body sensations in three patients.⁴³ Adverse effects after TES in animal studies have not been reported; however, one study addressed this concern and reported no negative effects up to 35 hours after application.³⁴ All other methods will, by nature of their invasiveness, be prone to various complications, depending on the location. The excellent safety profile is likely to be substantially lower in future clinical settings.

Challenges and Future Perspectives

A high number of recent reports demonstrate improvements in visual function by ES, which are expected to translate into large multicenter trials. The results from studies using different models of experimental animals have demonstrated favorable effects of ES on both the retina and optic nerve. However, the considerable problem with clinical studies so far has been the absence of randomization, a sham control, and inclusion of few patients. It is known that intra-individual changes in vision parameters vary significantly, common in neurorehabilitation; this makes it even more challenging in clinical trials. Another problem is that researchers all over the world experience the enormous advertising of stimulation prostheses and electrodes from many manufacturers because of considerable engineering and technical advances, making selection more difficult. As transpalpebral ES treatment is the only current treatment to show improved visual function in patients with AMD, more research to unravel the mechanisms behind its effects in an animal model is warranted. Such data are likely to yield clues on potential mechanisms of action using a transpalpebral approach as well as on how the advantageous effects on visual function in general can be further improved.

Stimulation parameters, such as current intensity, frequency, duration, and number of sessions, have been shown to vary in accordance with type of pathology and species.^{33,38} For example, in rats, the proposed current intensity of TES for protection of photoreceptors (300 μ A, 3 milliseconds per phase) is higher than that for survival of RGCs (100 μ A, 1 millisecond per phase).^{26,30} However, in humans, the threshold intensity required to elicit phosphene in both the central and peripheral visual fields is generally between 300 and 900 μ A.⁴⁴ Moreover, a study using positron emission tomography demonstrated that TES resulted in the activation of both retinotopographically matched primary visual cortex and visual perception in both normal-sighted persons and subjects with retinal degenerative disease.⁴⁴ However, the threshold current required to evoke phosphene is significantly lower in normal-sighted persons compared to patients with retinal degenerative disease.⁴⁷ Optimizing the ES parameters needed to achieve the ideal balance between the beneficial effects and adverse effects is required.

Conclusion

ES with the purpose of restoring limited vision and/or treating blindness has undergone enormous scientific advances during the past 10 years. The amount of evidence for restoring visual function in various diseases using ES is rapidly increasing. We have currently reached a stage where ES has moved into clinical practice. Its favorable safety profile is likely to boost progress in ES for treating eye

diseases. Still, there is a pressing need for a deeper understanding of the underlying mechanisms that govern clinical success. The optimization of stimulation parameters in animal studies, followed by large, prospective, clinical studies to explore the full potential of ES, is still required.

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