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Review

Transorbital Alternating Current Stimulation in Glaucoma: State of the Art from Neurophysiological Bases to Clinical Practice

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Abstract: Recovery after visual loss is a key goal of neuroscience and treatments able to improve visual function are still largely lacking. Glaucoma, one of the leading causes of visual disability in the world, is usually associated with elevated intraocular pressure (IOP), but a subset of "normal tension glaucoma" patients develop damage without ever manifesting high IOP. Sometimes, even in patients with good control of IOP, retinal ganglion cell degeneration can progress to forward blindness. Moreover, usually the damage already caused by the disease remains. These considerations underline the need to find new, effective treatments and solutions to add to the standard ones. In this paper, we expose the most important data supporting the use of alternating current stimulation, including the theoretical bases of this approach, in glaucoma.

Keywords: glaucoma; low vision; electrical stimulation

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1. Introduction

Recovery after visual loss is a key goal of neuroscience. However, treatments able to improve visual function are still largely lacking. Glaucoma is characterized by chronic neurodegeneration of the optic nerve. As one of the leading causes of visual disability in the world, glaucoma represents a major public health challenge and is a leading cause of irreversible blindness, creating problems with mobility, recognizing objects or faces, driving, reading, orienting, and secondary risks of depression, anxiety, and social isolation. With the aging of the population, increased life expectancy, and higher incidence of glaucoma in older persons, the number of patients with glaucoma is expected to increase considerably.

The term glaucoma does not refer to a single disease entity but rather to a group of optic neuropathies that share a common phenotype consisting of an excavated appearance of the optic nerve head and a loss of visual sensitivity that begins in the peripheral visual field. The cardinal event in the disease is the injury of retinal ganglion cells (RGCs) and their axons, leading to RGCs death by apoptosis and Wallerian degeneration of the axon between the eye and its central nervous system targets [1,2].

As with Alzheimer's and other neurodegenerative diseases, the loss of RGCs in glaucoma is slow, chronic, and progressive. The apoptosis caused by the activation of specific proteases, termed caspases, plays a pivotal role. Triggers of apoptosis in glaucoma include blockage of axonal transport, glutamate excitotoxicity, antibodies to heat shock proteins, ischemia, and vasoactive regulators such as nitric oxide.

Glaucoma is usually associated with elevated intraocular pressure (IOP), but a subset of "normal tension glaucoma" patients develop damage without ever manifesting high IOP. Clearly, IOP-dependent mechanisms, as well as IOP-independent mechanisms of RGC death are both present in glaucoma in different proportions. There is, in fact, substantial evidence from randomized trials that lowering IOP reduces the risk of progression of

primary open-angle glaucoma (POAG) and reduces the risk of conversion from ocular hypertension to POAG. IOP may be lowered by medical therapy (topical and systemic), laser therapy, and surgical procedures. However, even if the drugs and surgical procedures may block the degeneration of RGC, usually, the damage already caused by the disease remains. Moreover, sometimes, even in patients with good control of IOP, RGC degeneration can cause blindness to progress further. These considerations underline the need to find new, effective treatments and solutions.

2. The Residual Activation Theory

Recently, it has been postulated that there is some potential for vision restoration and recovery [3]. In fact, according to the "residual vision activation theory", visual functions can be reactivated and restored thanks to different structures spared, in part or completely, from the damage but unable to contribute much to the visual function. The scientific literature supports the idea that it is possible to engage these "residual" structures with different rehabilitative techniques, including electrical current stimulation, increasing their level of activation and thereby promoting visual improvement. In this light, if and to what extent vision restoration can be achieved is a function of the amount of residual tissue and its activation state.

According to the previous parallel with Alzheimer's disease, it was postulated that the early stages of some optic neuropathies, and in particular glaucoma, are characterized by failure of autoregulatory mechanisms to sustain normal RGC function under prolonged exposure to a stressful environment. Surviving RGCs have altered function, which may be reversible under less stressful conditions or otherwise cause cellular death if the stress factors continue to act. This hypothesis predicts that there will be a window between loss of function and loss of structure, during which RGC dysfunction can be modified with stress modulation; in other words, there will be an excess of RGC dysfunction compared with that expected from loss of tissue. In this condition, a further increase of stress (e.g., by increasing IOP in glaucoma) will worsen the disease, while a reduction of stress (e.g., by reducing IOP in glaucoma) will improve it (Figure 1).

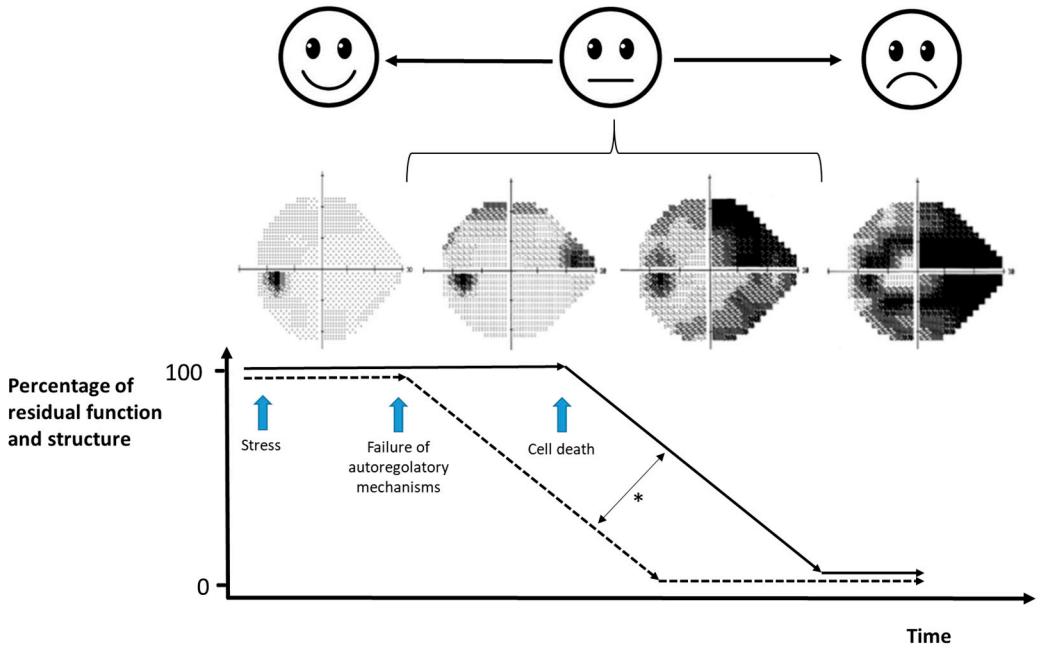

Figure 1. The picture summarizes the model proposed for glaucoma progression. The Figure, modified from Porciatti et al. 2012 [4], shows the mismatch (asterisk) between structural and functional impairment. After a prolonged stressful condition (the increase of IOP in the case of glaucoma), the autoregulatory mechanisms to sustain normal RGC function fail. The dysfunctional RGCs (straight face) can come back to a normal condition (smiley face) under less stressful conditions (or during

rehabilitating treatments, as for electrical stimulation) or otherwise proceed to death (frowny face) if the stress continues to act. X-axis: time course of the disease. Y-axis: percentage of residual function and structure. Continuous line: residual structure. Dashed line: residual function. Asterisk: mismatch.

This ability of RGCs to change their function over time in response to an environmental change can be defined as "retinal plasticity" and represents the rationale for treatment and a target to change the natural history of the disease [4].

Experimental data confirm this hypothesis. Amato et al. [5] found, in a DBA/2J mouse model of glaucoma, an inflammatory process involving Muller cells well before structural and functional alterations of RGC. Moreover, in the same study, by comparing electroretinogram (measuring retinal function) and optical coherence tomography (measuring RGC structure), the authors found RGC axon loss at 10 months of age, while the electroretinogram signal was altered about 3 months earlier. Similar observations were confirmed also in human glaucoma [3].

Falsini et al. [6] studied a group of patients with ocular hypertension and early glaucoma with pattern electroretinogram (PERG) and optical coherence tomography (OCT), representing objective tools to investigate, respectively, the function of RGC and their structure (as retinal nerve fiber layer thickness). The authors found in the group of patients with ocular hypertension no correlation between functional loss of RGCs and thickness of the retinal nerve fiber layer. However, they found a different scenario in more advanced cases of glaucoma, with a parallel and correlated loss of both PERG and retinal nerve fiber layer thickness.

3. Electrical Current Stimulation and Low Vision

Alternating current stimulation (trACS), usually performed with a trans-orbital montage but sometimes also trans-palpebral or trans-corneal, is becoming a new option for low vision restoration [7]. Data from studies on mouse models and MRI in humans demonstrate that, by delivering current with a transorbital montage, the vast majority of it flows through the eyeball and the optic nerve, not directly reaching the primary visual cortex [8]. In fact, it was shown that trACS could generate visually evoked potentials that can be inhibited in rats by blocking the RGC with tetrodotoxin [9], suggesting that the retina represents the entry gate for the current in the visual pathway and the brain [9].

According to literature and personal experience in the field, it is possible to consider two different effects of trACS. The first one is the "acute" effect of a single cycle of stimulation. In this case, the aim is to produce a rapid benefit for the patient (Figure 2).

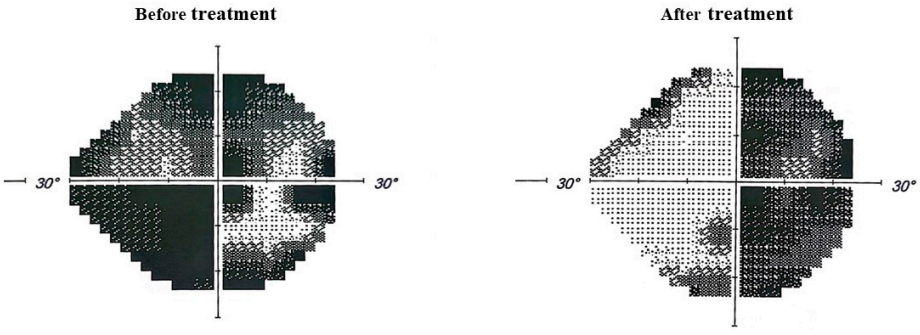

Figure 2. The Figure shows the visual field improvement of patients with retinitis pigmentosa before (**left**) and after (**right**) 10 consecutive days of trACS.

The acute effect is rather variable between patients, even those with the same pathology, probably reflecting the quantity of "silent" neurons and circuits along the visual pathway [8]. The presence and the amount of these silent areas can vary according to the different pathology affecting the patients, the severity of damage and, probably, individual factors that are still not clearly identified. According to the state of the art, it seems clear that trACS could enhance the functionality of neurons along the visual pathway by increasing

the coordination of firing and their excitability [1,8]. These mechanisms can be considered pathology-independent and can act provided the so-called "silent" or "awakened" neurons exist.

Electrical stimulation in pre-chiasmatic pathologies is now considered effective with a level A of evidence according to the results of different papers published in recent years, including a few randomized controlled trials. Nevertheless, this methodology is still not included in the routinary treatment of low vision [9–12].

The second possible effect of electrical stimulation is the "chronic" one, obtained with repeated cycles of stimulation over time. In this case, the aim is to produce a neuroprotection to slow retinal degeneration. Of course, this possibility should be considered only in the case of chronic neurodegenerative pathologies, such as glaucoma, or in the hyperacute phase of damage (as in the case of ischemic or mechanical damage). In fact, electrical stimulation of the eye can promote the activation of different cell survival pathways by modulating proteins [11] and genes [12] involved in cellular signaling, neuronal transmission, metabolism, and inflammation [13].

In particular, it was demonstrated [14,15] in rat models that electrical stimulation promotes gene expression, including potentially neuroprotective genes (such as Bax or other members of the tumor necrosis factor family), the release of growth factors (as FGF 2 and BDNF in whole retina [8,16] and IGF1, CNTF, and BDNF in retinal Muller cells [16–18]). Moreover, electrical stimulation can modulate L-type [19,20] voltage-dependent calcium channels [20,21], downregulate IL 1β and TNFα, and upregulate Bcl2 [18].

Finally, in the last few years, it has become clear that vision loss after optic nerve damage—a hallmark of glaucoma—leads not only to cell loss in the retina but also affects the whole visual pathway at the brain level. In fact, in addition to retinal changes, secondary changes in relay neurons of the lateral geniculate nucleus and of the primary visual cortex were demonstrated after retinal dysfunction [18,19,22]. Postretinal functional changes may either exacerbate those occurring at the RGC level or even mitigate them as a result of cortical compensatory mechanisms. In fact, a recent paper showed a reduction of power density, coherence, and connectivity of the high-alpha band (alpha II, 11–14 Hz) EEG activity in patients with low vision, with different types of pre-chiasmatic pathologies, in comparison to normal subjects. In the same group of patients, the loss of connectivity was related to visual perceptual capabilities, and trACS was able to partially reverse the EEG alterations in association with statistically significant clinical improvement [23].

4. Direct Evidence of Electrical Stimulation Efficacy in Glaucoma

There is some direct evidence in the literature supporting the role of electrical stimulation in glaucoma [24]. The most comprehensive study is a retrospective evaluation recently published by Erb et al. [25], demonstrating a positive effect of trACS in 101 eyes of 70 patients followed for about one year. According to the published classification of glaucoma severity, 20 (19.8%), 22 (21.8%), and 59 (58.4%) eyes were respectively categorized as early, moderate, and advanced glaucoma [24]. In this study, each patient was stimulated for 10 consecutive days, excluding weekends, 40 min per day with follow-ups for one year. The baseline mean defect (MD) of the visual field before stimulation was 13.6 ± 6.9 dB with a Median of 14.0 dB. One year after electrical stimulation treatment, the median MD changed from 14.0 dB to 13.4 dB, with a statistically significant difference corresponding to an MD reduction within 1 year in all eyes ($p < 0.01$). In 64 eyes of 49 patients (63.4%), ΔMD (calculated by subtraction of value before and after stimulation) was 0 or negative, indicating a halt of vision loss progression or even a tendency to improve within 1 year after treatment.

Ota et al. reported similar data in a very small case series of four patients with open-angle glaucoma [26].

One of the main risk factors for the occurrence and progression of glaucoma is the increase of IOP. Oxidative stress and vascular damage play major roles in triggering apoptotic cell loss in these tissues [1–9]. Molecular alterations occurring in the ocular

anterior chamber during the early course of glaucoma trigger this cell loss. Electrical stimulation could play a role in reducing IOP, as demonstrated in a paper by Gil-Carrasco et al. [27].

Moreover, other evidence arising from animal studies support the hypothesis of a neuroprotective role of electrical stimulation in glaucoma.

Jassim et al. [28] applied transcorneal electrical stimulation (20 Hz frequency, biphasic square wave of 100 mA current intensity, 1 msec pulse duration) for 10 min per eye every three days over 8 weeks in a group of DBA2/J mouse model of glaucoma. The authors included in the study a control group of DBA2/J mouse models without electrical stimulation. The effect of stimulation on the visual system was evaluated by examining RGC survival, the integrity of the optic nerve, and perturbation in inflammation and metabolism.

While no difference was found with the RGC number, the authors showed a positive effect on axon survival in the group stimulated with electrical current compared with the control group. Moreover, compared to the control, they found a reduction in CD3+ T cells and Iba1+ microglia in the stimulated group, indicating a significant reduction of inflammation.

The authors also quantified the ratio of pAMPK to AMPK in the optic nerve and retina of control and stimulated groups, showing a significantly lower pAMPK/AMPK ratio in the stimulated group than in the control, meaning improved energy homeostasis.

Finally, the authors evaluated BDNF and its receptors, focusing on neurotrophin receptors TrkB and p75NTR. BDNF is vital for RGC survival, and BDNF-TrkB signaling promotes neuronal survival. On the contrary, p75NTR (neurotrophin receptor) is dysregulated in glaucoma models, and its activation has been shown to induce neuronal apoptosis. The authors found the same amount of BDNF in the stimulated and unstimulated groups. However, while the total amount of TrkB was unchanged with age or stimulation, the amount of p75NTR decreased in the stimulated group, and the activated pTrkB was higher only in the stimulated group, compared to the control one. For these reasons, the authors hypothesized that in the stimulated group, where p75NTR levels were reduced, more BDNF was available to activate and phosphorylate TrkB and induce survival signaling (Figure 3).

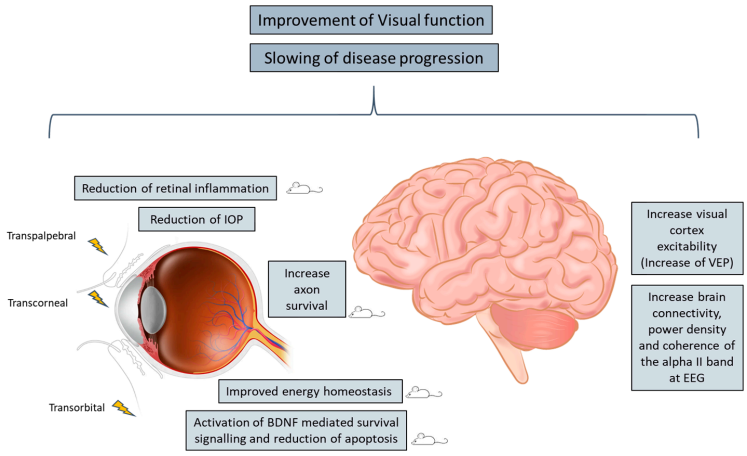

Figure 3. The Figure summarizes the different effects of electrical stimulation on the visual pathway (taking together transorbital, transcorneal, and transpalpebral montage). On the left are reported the effects of stimulation at the eye and optic nerve level. On the right are reported the effects at the brain level. The result of the stimulation is probably due to a combination of these mechanisms in different proportions according to the pathology, the severity of the clinical picture, and the personal predisposition. The clinical effect can be the improvement of visual function and, for chronic disease, the slowing of disease progression. The mouse symbol refers to data obtained only from animal experiments.

5. Discussion, Limitation and Open Issues

Recovery after visual loss is a key goal of neuroscience and treatments able to improve visual function are still largely lacking. In this scenario, the use of alternating current stimulation in low vision has become more and more important during the last two decades.

In this paper, we exposed the most important data supporting the use of this technique in glaucoma. The theoretical base of this approach is the possibility of promoting brain and retinal plasticity by using electrical stimulation.

Literature data, together with personal experience, ideally suggest that any patient, regardless of the pathology, can benefit from stimulation. Although the scientific support is still not strong enough to include this treatment in the guidelines for routine clinical practice [29], it must be admitted that many patients with glaucoma benefitted from this treatment. Clearly, the goal of this technique, as with many other rehabilitation and pharmacological treatments, is not the complete recovery of visual function, which was never reported in literature nor ever personally observed. This is because there is no chance of improvement for areas of the visual system having suffered complete structural degeneration.

Some points remain to be clarified. The variability of efficacy between patients is an issue that probably reflects the mismatch between functional impairment and structural degeneration, which was clearly demonstrated in glaucoma; the greater the mismatch, the greater the chance of improvement. However, there is no consensus about the right way to measure this mismatch in a single case, and even a clear demonstration that patients with significant mismatch are likely to respond is still missing. It is also still unclear which are the best parameters of electrical stimulation in terms of current intensity, frequency of stimulation, and duration of the treatment. Table 1 summarizes the clinical studies performed in patients with low vision, emphasizing the wide difference in stimulation parameters.

Table 1. Transorbital, Transpalpebral, Transcorneal ES: clinical studies.

Reference	Disease	Experimental Population	Stimulation Site	Frequency and Intensity	Type and Waveform	Duration	Days of Treatment
Anastassiou et al., 2013 [30]	Dry age-related macular degeneration	12 patients, 10 patients sham	Palpebral, both eyes	5–80 Hz; 150–220 μA	Transpalpebral-ES; waveform not indicated	Every session included 8 spots (40 s/spot)	5 days, 2 sessions on each day
Bola et al., 2014 [23]	Chronic prechiasmatic visual system damage	7 patients, 8 patients sham	Skin near the eyeball	Current strength above (125%) phosphene threshold as reported by the patients	rtACS; biphasic	40 min	10 days
Chaikin et al., 2015 [31]	Wet and dry age-related macular degeneration	17 patients, 25 eyes with dry type, 6 eyes with wet type	Palpebral, both eyes	3–162 Hz; 150 μA	rtACS	35 min	Once a week
De Rossi et al., 2020 [32]	Retinitis pigmentosa	6 patients	Over and below the eyeball	5–30 Hz; 1000 μA	rtACS	20–40 min	10 days
Granata et al., 2019 [1]	Optic atrophy	11 patients	Over and below the eyeball	10 Hz; 1 mA	rtACS	20 min	10 days
Granata et al., 2022 [33]	Chronic low vision	32 patients	Over and below the eyeball	10 Hz; 1 mA	rtACS	20 min	10 days
Erb et al., 2022 [25]	Glaucoma	70 patients, 101 eyes	Supraorbital and infraorbital	5–34 Hz; 1.2 mA	rtACS; biphasic	40 min	10 days

Table 1. *Cont.*

Reference	Disease	Experimental Population	Stimulation Site	Frequency and Intensity	Type and Waveform	Duration	Days of Treatment
Federov et al., 2011 [34]	Optic nerve damage	446 patients	Upper eyelide	5 Hz; intensity increase stepwise by 10 μA per second	rtACS; biphasic	25–40 min	10 days
Gall et al., 2010 [35]	Optic nerve damage	1 patient	On the eyelid in both eyes	10–30 Hz; <600 μA	rtACS; biphasic	30–40 min	10 days
Gall et al., 2011 [36]	Optic nerve damage	24 patients; 18 patients sham	Near the eyeball in both eyes	5 Hz; intensity increase stepwise by 10 μA per second	rtACS; pulse square or sinus	20–40 min	10 days
Gall et al., 2016 [37]	Optic nerve damage	45 patients, 37 patients sham	Near the eyeball in both eyes	Frequency not indicated; intensity +/−0.5 mA	rtACS	50 min	10 days
Gil-Carrasco et al., 2018 [27]	Open angle glaucoma	46 patients, 78 eyes	On the eyelid in both eyes	10 Hz, 100 μA	Transpalpebral-ES; biphasic	40 min	10 days
Ota et al., 2018 [26]	Open angle glaucoma	4 patients, 5 eyes	On the conjunctiva and the lower part of the cornea	20 Hz, 300 μA or 500 μA	rtACS; biphasic	30 min	Every 3 month, not indicates days
Rock et al., 2017 [38]	Open angle glaucoma	14 patients	Near the eyeball with DTL electrodes	20 Hz; intensity of current set on phosphene threshold	Transcorneal-ES; biphasic	30 min	One a week for 6 consecutive weeks
Sabel et al., 2011 [39]	Optic nerve damage	12 patients, 10 patients sham	Near the eyeball	0.5–25 Hz; <1000 μA	rtACS	15 min	10 days
Schmidt et al., 2013 [40]	Prechiasmatic partial optic nerve damage	18 patients, 6 patients sham	Orbital, both eyes	9–37 Hz; maximal amplitude <500 μA	rtACS	25–40 min	10 days
Shinoda et al., 2008 [41]	Wet and dry age-related macular degeneration	Palpebral, both eyes	21 patitents, 16 (27 eyes) with wet and 5 (7 eyes) with dry type	290 Hz for 1 min, 31 Hz for 2 min, 8.9 Hz for 10 min, 0.28 Hz for 7 min; 800 μA	Transpalpebral-ES; monophasic	20 min	4 times per day for up to 1 month

In this light, it is interesting to report the results of a paper published by D. K. Freeman et al. [42]. The paper explored the effects of different stimulation parameters for the selective activation of individual classes of neurons or targeting specific neuronal substructures. The study was conducted on retinal tissue isolated from sacrificed rabbits. The rationale of the paper is that the electric membrane properties of different neurons and neuronal substructures (e.g., soma vs. axon) vary considerably in terms of types and densities of voltage-gated ion channels, input resistance, capacitance, and synaptic contacts. The authors tested a train of sinusoidal stimuli with different frequencies, i.e., 5 Hz, 10 Hz, 25 Hz, and 100 Hz.

First, the authors showed that at each frequency, the activation of retinal ganglion cells was higher if the stimulus was applied at the soma than the distal axon. Moreover, they demonstrated that the response of ganglion cells at 5–10 Hz was greatly reduced with the application of an antagonist of AMPA/kainate receptors and completely blocked by using cadmium to block all synaptic transmission, indicating that the activation of ganglion cells in this range of frequency is mediated by synaptic transmission. The authors also showed the theoretical possibility of activating separately two different populations of ganglion cells, OFF and ON-ganglion cells. In fact, they demonstrated that OFF ganglion

cells tend to respond more during the cathodal phase of the sinusoidal stimulus for 5 Hz stimulation, while ON-ganglion cells tend to respond more during the anodal phase at the same frequency of stimulation. Because ON and OFF ganglion cells are thought to have similar intrinsic properties, the authors concluded that the mechanism responsible for this ON and OFF difference originates at a site presynaptic to ganglion cells, indicating as the more likely site of activation, the photoreceptor-to-bipolar cell synapse, where the ON and OFF pathways diverge. Since the same behaviours were not evident at 10 Hz, the authors suggested that the more likely site of activation at this frequency was the bipolar-to-ganglion cell synapse. Moreover, the response of ganglion cells to stimulation at 25 Hz after the application of an antagonist of AMPA/kainate receptors and cadmium was reduced but not completely abolished, indicating a residual activity probably not mediated by synaptic transmission. Finally, the response of ganglion cells at 100 Hz was not significantly affected by the application of synaptic blockers, meaning that at this frequency, the activation of ganglion cells was direct and independent of synaptic transmission. Thanks to these experiments, the authors concluded that different classes of retinal neurons can be targeted with the appropriate modulation of stimulus frequency: photoreceptors at 5 Hz, bipolar cells at 10–25 Hz, and ganglion cells at 100 Hz.

The results of this study are very interesting, but the possible practical implications have yet to be tested. If also confirmed in humans and in a clinical contest, it will be great to have the possibility to stimulate a precise population of retinal cells according to the pathology, for example, targeting more the photoreceptors in pathologies like the retinitis pigmentosa or the retinal ganglion cells in glaucoma.

In the last years, a plethora of tissues have been engineered (e.g., skin, bone cornea, heart), and many efforts are ongoing to create more complex functional tissue as neural ones, including the retina. In this light, in order to create more complex structures from simple two-dimensional (2D) cultures, different labs created more complex three-dimensional (3D) engineered tissue models and organoids resembling more closely the physiological structure and function of neural and retinal tissue. Moreover, new insight allowed the creation of the so-called microfluidic platform (or lab-on-a-chip), more simple with 3D models but with a higher 2D complexity than conventional 2D models. All these ex vivo models, also considering further improvements, could be very helpful in order to increase the knowledge about the pathophysiological mechanism and the effect of trACS [43,44].

It is quite clear that the positive effect of the stimulation in some cases decreases over time and increases the need to repeat the treatment, but there is no consensus about the frequency of stimulation cycles. Even if the idea of a personalized treatment (in terms of intensity and frequency of the current, shape of the stimulus wave, duration, and frequency of the stimulation cycles) is fascinating, state of the art still does not demonstrate a real benefit for personalized treatment in the single case. Another open issue is the effect of trACS over non-neuronal elements, such as Muller and glial cells [45]. Moreover, vascular dysregulation is a well-known problem in patients with glaucoma [46], and the increase in chorioretinal blood flow could be theoretically beneficial in this pathology and in ischemic retinal diseases. For this purpose, T. Kurimoto et al. [47] showed that trACS is able to increase the chorioretinal blood flow in normal subjects, and we believe this is an aspect that should be further studied.

Another broad field that should be better explored is the possibility of combining with trACS other existing rehabilitative techniques. For example, De Rossi et al. [32] explored the effect of combining visual pattern stimulation (VPS) with trACS in a very small trial. Six patients affected by retinitis pigmentosa were allocated into two groups, one performing only trACS and the other trACS and VPS together. The authors reported a visual improvement in both groups with a better trend in visual function recovery in the group combining trACS and VPS. To the best of our knowledge, there are no other studies exploring the combination of electrical stimulation with other rehabilitation techniques in humans. However, this is a fascinating suggestion that is important to explore more extensively.

The timing of stimulation should be another issue to explore. In fact, it is possible to figure out that a stimulation performed in the hyperacute phase of damage can be more effective than the same stimulation in the chronic phase, at least in some pathologies. For this purpose, Henrich-Noack et al. [48] demonstrated that trACS performed in a mouse model just after a traumatic optic nerve crush is effective in avoiding the wide loss of retinal ganglion cells due to retrograde Wallerian degeneration. The authors concluded that, early after trauma, trACS protects neurons from excitotoxic cell death. Translated in a clinical context, this could mean, for example, that trACS should be performed as soon as possible after optic nerve trauma and ischemic conditions to reduce the cellular loose in the ischemic penumbra.

6. Conclusions and Future Directions

The efficacy of electrical stimulation of the visual system with alternating current (applied with a transorbital montage or similar montage as transpalpebral or transcorneal) in low vision patients is supported by many scientific reports. However, the number of randomized controlled trials in this field is still very low, and the existing ones suffer from some limitations, mainly the low number of subjects enrolled and the inclusion of patients with different pathologies (patients with low vision caused by different diseases instead of a single pathology).

Therefore, we need more effort to improve the actual knowledge, designing new randomized controlled trials focused on glaucoma with a higher number of patients and rigorous inclusion criteria. Another issue arising from the literature and from the clinical experience is the great variability of trACS efficacy. Nevertheless, the knowledge already available ideally suggests that patients with glaucoma can benefit from the stimulation, and in this pathology, trACS should be considered as an additional arrow in the quiver, at least in the absence of other possible treatments.

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