AMERICAN ACADEMY OF OPHTHALMOLOGY®

Transorbital Alternating Current Stimulation in a Double-Masked Randomized Clinical Trial: Visual Functional Effect and Quality of Life

Maria de los Angeles Ramos Cadena, MD,[1] Ashley Sohn, MD,[1] Heather Livengood, PhD,[2] Ting-Fang Lee, PhD,[1,3] Batsheva Rubin, BA,[4,5] Jiyuan Hu, PhD,[1,3] Bernhard A. Sabel, PhD,[6] Rachel Matayev, BA,[1] Joseph Panarelli, MD,[1] Gadi Wollstein, MD,[4,7] Joel S. Schuman, MD[4,5,7,8]

Purpose: To determine the efficacy and safety of repetitive transorbital alternating current stimulation (rtACS) treatment by assessing vision-related quality of life and visual function outcome in subjects treated with rtACS versus sham-control.

Study design: Double masked, randomized, sham-controlled clinical trial (NCT03188042).

Subjects: Sixteen subjects with moderate-to-advanced glaucoma (visual field [VF] mean deviation [MD] ≤ -6.00 decibels) randomized into sham (9 subjects) or rtACS intervention (7 subjects) groups.

Methods: Subjects underwent 10 rtACS sessions over 2 weeks. All subjects had comprehensive ocular examination at baseline, 1-week, and 4-weeks posttreatment.

Main Outcome Measures: Visual acuity (VA), contrast sensitivity (CS), VF MD, number of threshold sensitivity points that changed or were unchanged, and vision-related quality of life (VR-QoL) questionnaire scores.

Results: The rtACS group showed a significantly greater improvement from baseline to 4 weeks posttreatment compared with sham in VR-QoL domains including near activities ($P < 0.01$), dependency ($P = 0.03$), social functioning ($P = 0.03$), mental health ($P < 0.01$) and in the overall composite score ($P = 0.04$). No significant changes were detected with VA, CS, and VF analyses for either group. No serious adverse events were noted in either study group.

Conclusions: Repetitive transorbital alternating current stimulation therapy showed a significant beneficial effect on several domains of VR-QoL. Further studies will determine its utility in glaucoma.

Financial Disclosure(s): Proprietary or commercial disclosure may be found in the Footnotes and Disclosures at the end of this article. *Ophthalmology Science 2025;5:100614 © 2024 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Glaucomatous damage to the structures of the visual pathway results in vision loss and impairment in vision-related quality of life (VR-QoL).[1] The National Eye Institute Visual Functioning Questionnaire (NEI VFQ) is a validated and standardized instrument that can be used to quantify subjective VR-QoL in individuals with glaucoma.[2–6] The full questionnaire consists of 42 questions, but the 39-item (NEI VFQ-39) version has been demonstrated to assess VR-QoL in glaucoma.[6]

Repetitive transorbital alternating current stimulation (rtACS) is a noninvasive brain stimulation that applies weak ($\leq$2 mA) oscillatory electrical currents with varying polarity and intensity through electrodes placed along the orbit and delivered to the visual pathway within the central nervous system.[7–9] It has been previously reported that repeated sessions of rtACS result in functional improvement of the visual system, presumably by promoting long-term adaptive plasticity.[10–13] The underlying mechanism of action is thought to be neuromodulation of oscillatory brain activity to improve synchronized brain wave synchronization via entrainment of alpha frequencies at occipital sites in subjects with optic neuropathies.[11–14] The purpose of this clinical trial was to determine the efficacy of rtACS intervention assessed by VR-QoL and the visual function outcome in subjects treated with rtACS versus sham-control.

Methods

Subjects

Subjects with moderate-to-advanced glaucoma (visual field [VF] mean deviation [MD] ≤ -6.00 decibels) in $\geq$1 eye and mild-to-advanced glaucoma (≤ -3.00 decibels) in the contralateral eye, with VF defects present for no <6 months, and with the best-corrected visual acuity (BCVA) of 20/200 or better in $\geq$1 eye were enrolled to this study (Table 1). Subjects were excluded if they had previously received rtACS, if they had any optic neuropathy other than glaucoma, pathological nystagmus, retinal

https://doi.org/10.1016/j.xops.2024.100614
ISSN 2666-9145/24

Table 1. Baseline Characteristics Reported as Mean (Standard Deviation) or Median (Quartiles)

	Sham	rtACS	
Subjects	9	7	*P* Value
Age (yrs)	65.7 (7.6)	67.9 (8.0)	0.575
Female, n (%)	4 (44%)	3 (43%)	1.000*
VF 24-2 MD (*dB*)	−17.86 (−25.66 to −10.15)†	−15.15 (−21.95 to −8.85)†	0.503
VFI	46.67 (34.74)	53.14 (31.24)	0.580
VF 10-2 MD (*dB*)	−17.47 (−28.84 to −7.91)†	−13.84 (−25.17 to −5.15)†	0.378

dB = decibels; MD = mean deviation; rtACAS = repetitive transorbital alternating current stimulation; VF = visual field; VFI = visual field index.
P value: 2-sample *t* test.
*Fisher exact test.
†Median (Quartile1; Quartile3).

comorbidities, vision loss associated with chronic and/or end stage diseases, metastatic cancer, electronic and/or metallic implants, seizures within the past 3 years, mental and/or psychiatric diseases, or glaucoma or any other intraocular surgeries within 3 months of enrollment. Qualified participants were randomized into sham (control) or rtACS intervention groups. All subjects were receiving hypotensive topical medication in ≥1 eye and continued their treatment throughout the study. All subjects, technicians, imagers, and physicians were masked to the randomization, except for the statistician randomizing. The research team was unmasked after the last enrolled subject completed the final follow-up (FU) visit and participants were informed as to which group they were assigned.

Written informed consent was obtained from all subjects and New York University School of Medicine Institutional Review Board/Ethics Committee approval was obtained. All subjects were treated in adherence to the tenets of the Declaration of Helsinki. The study was registered at ClinicalTrials.gov (NCT03188042) in January of 2017.

Study Design

In this prospective, randomized, sham-controlled, double-masked clinical trial qualified subjects underwent a comprehensive ocular examination, which included visual acuity (VA), contrast sensitivity (CS), VF tests, and the NEI VFQ-39 questionnaire. Subsequently, they were randomly assigned to either the treatment or sham groups. All participants underwent 10 treatment or sham sessions within a 2-week period.

A week after the final treatment or sham session (postintervention [PI] session), participants underwent the complete testing battery, as described at baseline. This battery of tests was repeated again 1 month after the final treatment or sham session (FU session).

Visual Acuity and CS

Best-corrected VA (BCVA) was measured with the Snellen chart at 6 meters and the ETDRS chart with illuminated light box at 3 meters. Scores were converted to logarithm of the minimum angle of resolution. Contrast sensitivity with corrected vision was measured with the Pelli-Robson chart at 1 meter using forced choice letter-by-letter scoring.

Visual Field Testing

Visual field testing was performed using Swedish interactive thresholding algorithm Standard 10-2 and 24-2 programs (Humphrey Field Analyzer; Zeiss). Qualified VFs had <33% false positives, negatives, and fixation losses. Visual field MD visual field index (VFI) scores and point-by-point threshold values were recorded every visit.

NEI VFQ-39

The NEI VFQ-39 questionnaire was administered verbally to each subject to document the self-reported VR-QoL. The 12 subscales in the NEI VFQ-39 include general health, general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision and peripheral vision.[6] Each subscale was scored on a 0 to 100 range, where 100 represents the best possible score. The overall composite score is an average of the responses to all subscales except for the general health questions. The general health subscale is an unweighted stand-alone scale as a marker of overall health status.

Sham and rtACS Interventions

Patients were assigned to either the rtACS or the sham group by stratified block randomization. This method ensures balance in the distribution of disease severity among the groups. In this study, the severity of glaucoma defined by the VF MD at baseline was considered as a potential prognosis factor and considered in the randomization.

Both rtACS and sham stimulation subjects were prepared using NuPrep abrasive gel (Weaver and Company) to remove excess oils from the skin. A rubber strap was placed around the head to hold the 2 3 × 3-cm neuroConn stimulation electrodes (Ilmenau) inserted into sponge pads and they were placed above each eye aligning the midline of the electrode with the center of the pupil. The rubber straps for the 5 × 7-cm neuroConn reference electrode covered by a sponge were placed around the right wrist. The sponges were soaked with saline an hour before the scheduled session. Stimulation was delivered with the neuroConn direct current stimulator multichannel device. The stimulation was delivered in a dark room as the frequency activity is dominant during dark conditions.[15] The alternating current wave type was sine, the frequency was standardized at 10 Hz across all interventions, and the range of amplitude was 450 to 1500 microamperes (μA). The stimulation duration was 30 minutes for the first week (5 sessions) and increased to 40 minutes for the second week (5 sessions). The amplitude was increased by 1 level (predetermined levels of amplitude) every 2 interventions throughout the 10 intervention sessions. The increase in time and amplitude safely maximized the subject's exposure to the stimulus. Subjects were asked before and after each intervention to report any adverse events.

Statistical Analysis

The 2-sample *t* test was used to test the differences in BCVA and CS between and within the sham and rtACS groups at baseline, PI, and FU. The changes from baseline to PI and FU between the sham and rtACS groups were compared using linear regression models.

To evaluate visual function, 24-2 and 10-2 VF were assessed, comparing between groups and the change from baseline to PI and FU visits. Visual field MD and the VFI were analyzed followed by a point-by-point analysis. Each threshold value at the PI and FU visits were compared with the threshold value at the corresponding location at baseline and recorded as improvement, no change, or worsening. The same procedure was applied specifically to the vulnerable threshold points located at the immediate margin of the scotoma during the baseline visit.

To evaluate the effect of rtACS on quality of life, NEI VFQ-39 scores were compared between PI and baseline, and between FU and baseline using linear regression models, with adjustment for baseline scores.

Results

Sixteen subjects (14 rtACS treated eyes and 18 sham eyes) were enrolled. There were no significant differences in age and disease severity at baseline between the groups (Table 1). No difference was detected between groups in the presence of cataracts versus intraocular lens, presence of central scotoma in the 10-2 visual fields, as well as number of medications. Out of 32 enrolled eyes, 12 had glaucoma surgery in the past. All subjects tolerated the treatment without any adverse events.

The BCVA and CS values showed no statistically significant difference between groups from baseline at PI and FU visits (Table 2), but the overall trend in VA in the rtACS group was toward improvement in both PI and FU visits, whereas the sham group showed a slight deterioration in the FU visit. When change was evaluated within groups the rtACS treated subjects showed statistically significant improvement at the PI visit. Minimal change was noted in CS between and within groups over the FU period (Table 2).

The 24-2 VF MD and the VFI in the rtACS treated group improved from baseline to PI and continued improving at FU (Table 3). When evaluating the percentage of testing points demonstrating an improvement threshold sensitivity, there was a slight increase in the rtACS eyes and a decrease in the sham eyes from PI to FU visits. The percentage of unchanged points was similar in both groups at the PI and FU visits, but the percentage of worsened points increased in the sham group between PI and FU visits, while remaining at the same level in the rtACS group. Limiting the analysis to the vulnerable points, a higher percentage of points improved in the sham compared with the rtACS group at the PI visit, but this improvement was not sustained in the sham group at the FU session and remained at the same level for the rtACS group. Approximately the same percentage of points remained unchanged or worsened across the groups in both time points, but the percentage of worsened points in the sham group increased between PI and FU visits while remaining at the same level for the rtACS group. No statistical significance was detected for any of these comparisons between the groups.

The 10-2 VF MD showed improvement in both groups at the PI and FU visits, and the difference was more noticeable in the sham group (Table 3). However, evaluating the change at individual testing point level showed the opposite trend than the one observed with 24-2. A smaller percentage of points improved in the rtACS group compared with the sham group and there was an increase of the percentage of points which were getting worse at FU compared with PI visits. The vulnerable points analysis showed larger improvement in the sham compared with the rtACS group. No significant difference was detected between the groups.

Assessment of the quality of life showed no significant difference between the 2 groups at baseline (except for marginal difference in general health) and the change from baseline to the PI visit in the composite score and all domains (Table 4). However, the rtACS group showed a

Table 2. Visual Acuity and Contrast Sensitivity in the Sham and rtACS Groups in Baseline, Postintervention and Follow-up Visits, Change between Baseline, Postintervention and Follow-up

	Sham n = 18 Eyes	*P* Value within Groups	rtACS n = 14 Eyes	*P* Value within Groups	*P* Value between Groups
Visual Acuity					
Baseline	0.16 (0.16)		0.08 (0.13)		0.14
PI	0.16 (0.17)		0.10 (0.14)		0.34
FU	0.13 (0.14)		0.11 (0.13)		0.58
PI - baseline	0.0032 (0.0915)	0.88	0.0284 (0.0475)	**0.04**	0.36
FU - baseline	−0.0233 (0.1349)	0.47	0.0297 (0.0622)	0.09	0.18
Contrast Sensitivity					
Baseline	1.26 (0.47)		1.40 (0.42)		0.40
PI	1.08 (0.55)		1.39 (0.35)		0.08
FU	1.30 (0.47)		1.39 (0.39)		0.54
PI - baseline	−0.1750 (0.6117)	0.24	−0.0036 (0.1184)	0.91	0.31
FU - baseline	0.0417 (0.1768)	0.33	−0.0036 (0.1562)	0.93	0.46

FU = follow-up; PI = postintervention; rtACAS = repetitive transorbital alternating current stimulation.
Data reported as mean (standard deviation).
Bolded values represent statistical significance ($P < 0.05$).

Table 3. Change from Baseline in the Visual Field for Sham and rtACS Groups

		Baseline to PI		Baseline to FU	
		Sham	*rtACS*	*Sham*	*rtACS*
24-2 VF					
Change in MD *dB*		1.01 (3.40)	0.25 (1.81)	−0.01 (4.42)	0.46 (1.57)
Change in VFI		2.89 (9.65)	0.86 (6.27)	0.39 (16.13)	2.00 (6.58)
Change in threshold sensitivity points % (SD)	Improved	30 (19)	29 (13)	25 (20)	31 (14)
	Unchanged	48 (19)	47 (14)	47 (24)	46 (16)
	Worsened	22 (18)	23 (11)	27 (24)	23 (11)
Change in number of vulnerable points % (SD)	Improved	47 (26)	43 (18)	38 (22)	44 (18)
	Unchanged	24 (13)	26 (16)	29 (21)	27 (16)
	Worsened	28 (19)	31 (17)	33 (28)	30 (22)
10-2 VF					
Change in MD *dB*		1.10 (2.24)	0.72 (2.06)	1.14 (1.55)	0.56 (2.53)
Change in threshold sensitivity points % (SD)	Improved	31 (20)	26 (14)	32 (17)	25 (16)
	Unchanged	49 (17)	54 (15)	49 (17)	50 (15)
	Worsened	20 (16)	19 (11)	19 (14)	25 (9)
Change in number of vulnerable points % (SD)	Improved	45 (20)	37 (20)	53 (22)	42 (24)
	Unchanged	24 (16)	37 (16)	22 (17)	31 (16)
	Worsened	31 (18)	25 (15)	26 (16)	27 (19)

dB = decibels; FU = follow-up. MD = mean deviation; PI = postintervention; SD = standard deviation; VF = visual field; VFI = visual field index.

significantly larger improvement from baseline to FU compared with the sham group in the overall composite score and 4 domains: near activities, social functioning, mental health, and dependency.

Discussion

In this prospective, double-masked, randomized, sham-controlled clinical trial, the VR-QoL of the rtACS group showed a significant improvement at FU in 4 domains and the composite score of the NEI VFQ-39 compared with the sham group, which showed no significant differences at PI and FU. Visual function showed inconsistent trends with 24-2 and 10-2 VF testing protocols.

It has been described that when stimulating VF borders by rtACS, significant reduction of the size of the scotoma may be achieved in a noninvasive manner.[10,16,17] Fedorov et al[10] reported that larger eccentricities of outer VF borders were observed in 55.3% of the subjects and enlargements of VF size in 40% of the subjects treated with rtACS. Gall et al[12] also observed a significant improvement in the rtACS group in sections of the VF where expansion was expected, as well as a reduction in the defect depth. These VF changes were still present after a 2-month FU period, and the greater the VF changes, the

Table 4. Baseline Scores of the Quality of Life Questionnaire and Mean Difference from Baseline to Postintervention and to Follow-up with Comparison between the Groups

	Baseline			Baseline to PI			Baseline to FU		
Domain	*rtACS*	*Sham*	*P**	*rtACS*	*Sham*	*P*†	*rtACS*	*Sham*	*P*‡
Composite score	81.2 (14.2)	74.2 (12.4)	0.32	3.52 (6.86)	0.95 (4.43)	0.17	3.87 (4.60)	1.97 (7.89)	**0.04**
General health	84.6 (7.5)	66.1 (20.0)	0.05	−4.58 (10.40)	6.11 (9.93)	0.25	−4.58 (5.57)	6.94 (9.75)	0.20
General vision	64.2 (14.6)	50.6 (15.3)	0.11	3.33 (12.10)	3.89 (14.30)	0.73	9.17 (12.00)	18.30 (23.80)	0.99
Ocular pain	89.6 (5.1)	84.7 (17.4)	0.52	2.08 (12.30)	0.00 (16.50)	0.51	4.17 (6.45)	2.78 (18.50)	0.44
Near activities	79.9 (19.4)	75.9 (15.1)	0.66	3.47 (7.18)	−1.85 (8.36)	0.19	7.64 (9.65)	−3.70 (11.30)	**<0.01**
Distance activities	80.3 (20.6)	72.3 (21.8)	0.49	5.83 (10.80)	1.57 (8.51)	0.21	3.06 (6.60)	5.46 (10.70)	0.91
Social functioning	93.1 (9.74)	89.8 (15.5)	0.66	0.00 (5.27)	1.85 (12.30)	0.96	6.94 (9.74)	0.00 (7.22)	**0.03**
Mental health	79.2 (15.0)	59.4 (21.4)	0.07	7.50 (12.90)	3.33 (9.35)	0.29	9.17 (7.36)	0.56 (17.00)	**<0.01**
Role difficulties	80.2 (23.9)	74.3 (13.1)	0.54	8.33 (17.50)	−4.17 (9.88)	0.06	1.04 (8.31)	−6.25 (13.60)	0.20
Dependency	91.7 (10.9)	86.8 (12.3)	0.45	3.12 (8.62)	−3.47 (5.51)	0.10	4.17 (5.10)	−2.08 (10.80)	**0.03**
Color vision	91.7 (12.9)	97.2 (8.33)	0.33	4.17 (10.20)	2.78 (8.33)	0.44	4.17 (10.20)	0.00 (12.50)	0.99
Peripheral vision	66.7 (37.6)	66.7 (30.6)	0.99	4.17 (10.20)	−2.78 (23.20)	0.49	−4.17 (24.60)	−2.78 (26.40)	0.90

FU = follow-up; PI = postintervention.
Bolded values represent statistical significance ($P < 0.05$).
*Comparison between groups at baseline.
†Comparison between groups of the change from baseline to PI.
‡Comparison between groups of the change from baseline to FU.

more pronounced was the improvement in the quality-of-life general vision subscale.[10] Similar to these reports, we observed in the rtACS group an improvement in VF 24-2 MD and VFI from baseline to PI and FU. In contrast, the sham group displayed an improvement at PI but then a deterioration at FU. It has been proposed that the improvement in VF of rtACS treated subjects is due to increased neuronal synchronization and coherent oscillatory activity via entrainment of alpha frequencies spreading over cortical areas with long-term after-effects.[7,10–12,15] However, in the 10-2 VF, the rtACS group did not exhibit improvement from the treatment in comparison with the sham group which might indicate a preferential peripheral effect with no benefit at central vision. It should be noted that none of the differences between the groups were statistically significant. Therefore, we cannot ascertain the benefit of the treatment on the VF.

It has been previously reported that subjects with glaucoma have difficulties with outdoor mobility, glare and lighting, household tasks, and personal care.[2,18] Furthermore, Szegedi et al[3] observed that as the disease progresses glaucoma subjects have lower scores in the general vision, near activities, distance activities, mental health, driving, and peripheral vision domains. In our study, subjects treated with rtACS reported an improvement in their VR-QoL because of the improvement in near activities, social functioning, mental health, and dependency domains (Table 4). In the near activities domain, treated subjects reported an improvement, described as less difficulty performing tasks like sewing, cooking, reading, recognizing medicine bottles, using hand tools, etc. In the social functioning domain, subjects in the rtACS group reported less difficulty at FU compared with baseline in activities like going out, visiting friends, noticing people's reactions and faces, etc. In the mental health domain treated subjects reported improvement described as less irritability and frustration because of their eyesight, embarrassment to self and others because of their vision, ability of doing things they enjoy, etc. Lastly, in the dependency domain, subjects in the rtACS group reported improvement in relying on what other people tell them, needing a lot of help because of their eyesight, or not being able to go out without help, etc. Although we cannot explain these improvements by changes in VA, CS or VF, this finding concurs with Gall et al[10] who also observed a significant improvement in the social functioning domain of the NEI VFQ-39 in the rtACS group. Further investigation is warranted.

The limitations of the study are that during the first and last 15 seconds of the intervention, both groups received rtACS. Although we attempted to minimize the effect by limiting the dose to only 30 seconds, there might be, at least a small therapeutic effect as a confounder in the sham group. Additionally, this pilot study was performed with a small cohort per group and a short FU period, which may play a role in the limited VF findings.

In conclusion, this double-masked, randomized, sham-controlled clinical trial showed a significant beneficial effect on several domains of quality of life, suggesting rtACS might be a valuable tool in the treatment of glaucoma. Larger cohorts and longer FU are needed to further evaluate the utility of rtACS in glaucoma.

Footnotes and Disclosures

Originally received: December 28, 2023.
Final revision: August 27, 2024.
Accepted: August 30, 2024.
Available online: September 4, 2024. Manuscript no. XOPS-D-23-00336R1.

[1] Department of Ophthalmology, NYU Langone Health, New York, New York.

[2] Division of Occupational Therapy, West Virginia School of Medicine, Morgantown, West Virginia.

[3] Department of Population Health, NYU Langone Health, New York, New York.

[4] Glaucoma Service, Wills Eye Hospital, Philadelphia, Pennsylvania.

[5] Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania.

[6] Medical Faculty, Institute of Medical Psychology, Otto-v.-Guericke University of Magdeburg, Magdeburg, Germany.

[7] Vickie & Jack Farber Vision Research Center, Wills Eye Hospital, Philadelphia, Pennsylvania.

[8] Science and Health Systems, Drexel University School of Biomedical Engineering, Philadelphia, Pennsylvania.

Disclosures:

All authors have completed and submitted the ICMJE disclosures form.

The author(s) have made the following disclosure(s):

B.A.S.: Royalties or licenses – SAVIR GmbH; B.A.S.: Consultant – SAVIR-Center GbR, SAVIR GmbH; Equity/stock – SAVIR-Center GbR and SAVIR GmbH; Travel support – SAVIR GmbH; Patents planned, issued or pending – Patent pending on a home-stimulation device which was not used in the present study; Leadership – International Council of Ophthalmology, Representative for the ISLRR as member of ICO voting council, Deutscher Hochschulverband (DHV) (German University Association, Chairman of State Chapter.

G.W.: Grants – NIH R01-EY030770; NIH R01-EY035174.

J.P.: Consultant – AbbVie, CorNeat, Aerie Pharma, Glaukos, Alcon, New World Medical, Avisi Technologies, Santen, Nova Eye Medical, Ocular Therapeutics, AOI Ophthalmics, Zeiss.

J.S.S.: Consultant – AEYE Health, Alcon Laboratories, Inc, Zeiss, Ocugenix, Ocular Therapeutix, Opticient, Perfuse, Inc; Equity/stock – AEYE Health, Ocugenix, Ocular Therapeutix, Opticient; Patents/royalty – Ocugenix.

The other authors have no proprietary or commercial interest in any materials discussed in this article.

Supported by NIH R01-EY013178 (Bethesda, MD), P30-EY013079, unrestricted grant from Research to Prevent Blindness.

Joel S. Schuman, MD, FACS, an editorial board member of this journal, was recused from the peer-review process of this article and had no access to information regarding its peer review.

HUMAN SUBJECTS: Human subjects were included in this study. Written informed consent was obtained from all subjects and New York University School of Medicine Institutional Review Board/Ethics Committee approval was obtained. All subjects were treated in adherence to the tenets of the Declaration of Helsinki.

No animal subjects were used in this study.

Author Contributions

Conception and design: Ramos Cadena, Livengood, Lee, Sabel, Panarelli, Wollstein, Schuman

Data collection: Ramos Cadena, Sohn, Livengood, Rubin, Matayev

Analysis and interpretation: Ramos Cadena, Lee, Hu, Wollstein, Schuman

Obtained funding: N/A

Overall responsibility: Ramos Cadena, Wollstein, Schuman

Abbreviations and Acronyms:
BCVA = best-corrected visual acuity; **CS** = contrast sensitivity; **FU** = follow-up; **MD** = mean deviation; **NEI VFQ** = National Eye Institute Visual Functioning Questionnaire; **PI** = postintervention; **rtACS** = repetitive transorbital alternating current stimulation; **VA** = visual acuity; **VF** = visual field; **VFI** = visual field index; **VR-QoL** = vision-related quality of life.

Keywords:
Neurostimulation, Glaucoma, Clinical trial.

Correspondence:
Gadi Wollstein, MD, Wills Eye Hospital, Rm 1535, 840 Walnut St. Philadelphia, PA 19107. E-mail: GWollstein@Willseye.org.

References

1. Gall C, Lucklum J, Sabel BA, Franke GH. Vision- and health-related quality of life in patients with visual field loss after postchiasmatic lesions. *Invest Ophthalmol Vis Sci*. 2009;50:2765−2776.
2. Goldberg I, Clement CI, Chiang TH, et al. Assessing quality of life in patients with glaucoma using the Glaucoma Quality of Life-15 (GQL-15) questionnaire. *J Glaucoma*. 2009;18(1):6−12.
3. Szegedi S, Boltz A, Scharinger EM, Vecsei-Marlovits PV. Quality of life in patients with glaucoma assessed by 39-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-39). *Graefes Arch Clin Exp Ophthalmol*. 2022;260:1623−1631.
4. Bola M, Gall C, Moewes C, et al. Brain functional connectivity network breakdown and restoration in blindness. *Neurology*. 2014;83:542−551.
5. Mangione CM, Berry S, Spritzer K, et al. Identifying the content area for the 51-item National Eye Institute Visual Function Questionnaire: results from focus groups with visually impaired persons. *Arch Ophthalmol*. 1998;116:227−233.
6. Nassiri N, Mehravaran S, Nouri-Mahdavi K, Coleman AL. National Eye Institute Visual Function Questionnaire: usefulness in glaucoma. *Optom Vis Sci*. 2013;90:745−753.
7. Perin C, Vigano B, Piscitelli D, et al. Non-invasive current stimulation in vision recovery: a review of the literature. *Restor Neurol Neurosci*. 2020;38:239−250.
8. Abd Hamid AI, Gall C, Speck O, et al. Effects of alternating current stimulation on the healthy and diseased brain. *Front Neurosci*. 2015;9:391. https://doi.org/10.3389/fnins.2015.00391.
9. Zaghi S, Acar M, Hultgren B, et al. Noninvasive brain stimulation with low-intensity electrical currents: putative mechanisms of action for direct and alternating current stimulation. *Neuroscientist*. 2010;16:285−307.
10. Fedorov A, Jobke S, Bersnev V, et al. Restoration of vision after optic nerve lesions with noninvasive transorbital alternating current stimulation: a clinical observational study. *Brain Stimul*. 2011;4:189−201.
11. Schmidt S, Mante A, Ronnefarth M, et al. Progressive enhancement of alpha activity and visual function in patients with optic neuropathy: a two-week repeated session alternating current stimulation study. *Brain Stimul*. 2013;6:87−93.
12. Gall C, Schmidt S, Schittkowski MP, et al. Alternating current stimulation for vision restoration after optic nerve damage: a randomized clinical trial. *PLOS ONE*. 2016;11:e0156134. https://doi.org/10.1371/journal.pone.0156134.
13. Wu Z, Sabel BA. Spacetime in the brain: rapid brain network reorganization in visual processing and recovery. *Sci Rep*. 2021;11:17940. https://doi.org/10.1038/s41598-021-96971-8.
14. Sabel BA, Thut G, Haueisen J, et al. Vision modulation, plasticity and restoration using non-invasive brain stimulation − an IFCN-sponsored review. *Clin Neurophysiol*. 2020;131:887−911.
15. Kanai R, Chaieb L, Antal A, et al. Frequency-dependent electrical stimulation of the visual cortex. *Curr Biol*. 2008;18:1839−1843.
16. Kasten E, Muller-Oehring E, Sabel BA. Stability of visual field enlargements following computer-based restitution training − results of a follow-up. *J Clin Exp Neuropsychol*. 2001;23:297−305.
17. Gall C, Fedorov AB, Ernst L, et al. Repetitive transorbital alternating current stimulation in optic neuropathy. *Neuro-Rehabilitation*. 2010;27:335−341.
18. Nelson P, Aspinall P, O'Brien C. Patients' perception of visual impairment in glaucoma: a pilot study. *Br J Ophthalmol*. 1999;83:546−552.