Noninvasive transorbital alternating current stimulation improves subjective visual functioning and vision-related quality of life in optic neuropathy

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Background
Noninvasive repetitive transorbital alternating current stimulation (rtACS) can improve visual field size in patients with optic nerve damage, but it is not known if this is of subjective relevance. We now assessed patient reported outcomes to determine the association between visual field changes and vision-related quality of life (QoL).

Methods
Patients having visual field impairments long after optic nerve damage (mean lesion age 5.5 years) were randomly assigned to a rtACS (n = 24) or sham stimulation group (n = 18). Visual fields and patient reported outcome measures (vision-related QoL: National Eye Institute Visual Function Questionnaire, NEI-VFQ and health-related QoL: Short Form Health Survey, SF-36) were collected before and after a 10-day treatment course with daily sessions of 20 to 40 minutes. The primary outcome measure was the percent change from baseline of detection ability (DA) in defective visual field sectors as defined by computer-based high resolution perimetry (HRP). Secondary outcome parameters included further HRP parameters as well as static and kinetic perimetry results. Changes in QoL measures were correlated with changes in primary and secondary outcome measures in both groups.

Results
DA increase in the defective visual field was significantly larger after rtACS (41.1 ± 78.9%, M ± SD) than after sham stimulation (13.6 ± 26.3%), P < 0.05. While there was a significant increase of DA in the whole tested HRP visual field after rtACS (26.8 ± 76.7%, P < 0.05), DA in sham-stimulation
patients remained largely unchanged (2.7 ± 20.2%, ns). Results of secondary outcome measures (static and kinetic perimetry) provided further evidence of rtACS efficacy. Improvements in NEI-VFQ subscale “general vision” were observed in both groups but were larger in the rtACS group (11.3 ± 13.5, Z = −3.21, P < 0.001) than in the sham group (4.2 ± 9.4, Z = −1.73, P < 0.05) with a significant difference between groups (Z = −1.71, P < 0.05). DA change and some NEI-VFQ domains were correlated (r = 0.29, P < 0.05), but no significant correlations were observed between DA and SF-36 results.

Conclusions

rtACS facilitates vision restoration after unilateral, long-term optic nerve lesion as assessed both by objective DA changes and improvements in some NEI-VFQ subscales. Both were positively but low correlated, which suggests that factors other than visual field size also contribute to improved vision-related QoL.

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Keywords quality of life; alternating current stimulation; vision recovery; plasticity; optic neuropathy

Visual field defects caused by optic nerve or visual cortex damage are responsible for substantial limitations in vision-related activities in everyday life and restrictions of vision-specific quality of life (QoL). Visual deficits can spontaneously recover to some extent within the first weeks and months after the injury, but spontaneous improvements of visual acuity in untreated patients after optic nerve trauma, for example, occur only in about 50% of cases at 3 months postlesion. The remaining partial blindness after this early recovery phase is considered permanent. Because so far all therapeutic interventions including corticosteroid therapy or optic canal decompression surgery were not found to be effective to leave patients without chronic visual deficits, there is a need to find new treatment procedures at the chronic stage.

As recent studies have shown, patients with optic nerve damage can achieve improvements of their visual fields well beyond the period of spontaneous recovery. In a single case study and in two sham-controlled clinical trials using a 10-day treatment course of noninvasive, repetitive transorbital alternating current stimulation (rtACS) of the brain with daily sessions of approximately 20 minutes per treated eye, we observed significant reductions of the scotoma size. This stimulation procedure was developed for patients with vision loss caused by lesions to the prechiasmatic visual pathway. The treatment procedure was based on electrical stimulation parameters that were used during invasive treatment of injured optic nerves during neurosurgery of partially or totally blind patients. Objective improvements of visual function, such as increases of visual acuity and/or larger eccentricities of outer visual field borders (measured by kinetic perimetry), were observed in about 55.3% of patients treated with rtACS and enlargements of visual field size after rtACS were observed in 40% of the treated patients. These findings are in agreement with the results of a small study applying electrical stimulation directly at the cornea of affected eyes in a few patients with optic neuropathies. In this study, increased visual acuity was also observed in six of eight treated eyes after only one session of electrical stimulation. In a single case study of a patient with traumatic optic neuropathy and initially absent P100 visual evoked potential showed such potential again after a 10-day course of rtACS. However, little is known if such “objective” detectable improvements of sight have a positive impact on every day life, though methods are available to quantify subjective vision-related QoL changes.

Subjective daily life impairments caused by visual field loss can be measured conveniently with the National Eye Institute Visual Function Questionnaire (NEI-VFQ). To our knowledge, there are no reports of therapy outcome measures and associated QoL changes in a patient group with loss of visual field size and visual acuity after prechiasmatic damage. Thus, it is unknown if existing QoL instruments are sensitive enough to document improved visual functions.

The current study was therefore carried out to address the question whether visual field improvements after rtACS treatment in patients with optic neuropathy are subjectively noticed by patients. To this end we have investigated visual fields and patient reported outcome measures (PROMs) in a pre-post study design. PROMs are traditionally measured using validated questionnaires with known psychometric properties. To measure the vision-related activity limitation, respectively vision-targeted QoL, the NEI-VFQ was selected for the current study.

Health-related QoL should be considered in pre-post designs because adjustment of vision-related measures for physical and mental components of general health perception may produce changes in the treatment effect measured with the NEI-VFQ. Therefore, health-related QoL estimates were obtained using the common generic Short Form Health Survey (SF-36). In a similar study conducted in our laboratory, 85 patients with predominantly postchiasmatic damage were investigated before and after 6 months of behavioral computer-assisted vision restoration training. This kind of
behavioral stimulation was found to improve visual fields in hemianopic patients after brain damage at the visual field borders. Similar behavioral approaches led to improvements even deep in the blind field. Visual field enlargements after training were accompanied by improvements in NEI-VFQ scores indicating that objective improvements of the visual field were subjectively relevant to the patients and that patient reported outcomes were sensitive to treatment effects.

One may argue that patients having undergone a long and laborious training for 6 months may be biased to report subjective visual improvements after such a time commitment. We therefore used a nontraining type therapy, rtACS, with the reasoning that it would be not prone to such training artefact when measuring subjective visual functioning and vision-related QoL, along with perceptual functioning, before and after treatment. We hoped that this would help clarifying the value of QoL instruments for clinical research but also further substantiate the efficacy of noninvasive current brain stimulation. The current study was therefore carried out to evaluate whether noninvasive rtACS may induce subjectively noticeable changes of self-estimated visual- and health-related functioning assessing PROMs with existing QoL instruments. RtACS led to partial restoration of visual fields that was accompanied by improvements of vision-related QoL (NEI-VFQ) and health-related QoL (SF-36).

Methods

Subjects

The current sample consisted of 42 subjects (29 males and 13 females). The data were pooled from two clinical trials that had a comparable study setting with a total sample of 59 patients. Of this total sample, 13 subjects failed to return the questionnaires. Two additional patients were excluded from further analyses because of unreliable visual field results in high-resolution perimetry (HRP) (too many false-positive reactions and low fixation control response rates). Two patients dropped out during diagnostic sessions after the treatment course was already completed and thus had to be excluded from the analysis.

All patients were treated according to the ethical standards of the Declaration of Helsinki (1964). Ethical approval was obtained from the local ethics committees. For self-assessment NEI-VFQ and SF-36 questionnaires were sent to the patients by mail. All patients were informed that answering the questionnaires was voluntary. Patients were asked to answer the questionnaires without help. All subjects included in the study were able to comprehend the questions of the NEI-VFQ and SF-36.

Patients who returned the questionnaires and thus were included in this study were older (57.1 years; SD = 13.6; range 26-74) than those who did not return the questionnaires (42.9 years; SD = 15.0; range 20-70; T = -4.31, P < 0.0001. There were no differences between the two patient samples in lesion age (see below), baseline ophthalmologic results as well as primary or secondary outcome results (two-tailed t tests). Thus, the study results can not be explained by a sampling bias.

The main criterion for inclusion in the data analysis was visual field loss because of damage of the optic nerve with at least some detectable amount of residual vision. Exclusion criteria were heart pacemakers, epileptic seizures within the last 3 years, photosensitive epilepsy as determined by EEG, psychiatric diseases (schizophrenia), diabetes causing diabetic retinopathy, high blood pressure, macular degeneration, instable or high level of intraocular pressure (more than 27 mm of HG column) or total blindness.

Etiologies were nonarteritic anterior ischemic optic neuropathy (AION) (n = 8) or arteritic AION (n = 8), postinflammatory (n = 4) or posttraumatic optic neuropathy (n = 5), optic atrophy in the course of glaucomatous optic neuropathy (n = 4), compressive optic neuropathy because of meningeoma (n = 3) or pituitary tumor (n = 1), chronic papilledema after pseudotumor cerebri (n = 1), optic neuropathy after hemorrhagic stroke (n = 2), or idiopathic optic atrophy (n = 6). In the majority of patients both eyes had visual field defects (n = 28).

The mean lesion age at the beginning of this study was 69 months (SD = 81) with no significant difference between groups (T = -0.47, P = 0.638).

Patients were randomly assigned to either the rtACS (n = 24) or sham group (n = 18). The groups significantly differed by age (T = 2.85, P < 0.01). Mean age of sham patients was 62.9 years (SD = 7.0; range 53-74). Mean age of rtACS patients was 52.7 years (SD = 15.7; range 26-74).

Study design

Pre- and post-treatment diagnostics were carried out by study nurses who were blind concerning the treatment arm to which the patients were assigned. Baseline diagnostics of visual function parameters and PROMs was conducted the week before treatment started. After completion of the baseline diagnostics, patients were randomized by lot to the rtACS or sham group. Stimulation was applied daily for 2 weeks (excluding weekend), i.e., for a total of 10 days. The length of the daily treatment session (both rtACS and sham treatment) was between 10 to 20 minutes for each eye, i.e., a maximal 40 minutes. Final diagnostics of visual function parameters and PROMs was conducted the week after the last treatment session (the earliest 48 hours later). Patients were asked to participate in a second follow-up 8 weeks after stimulation (Supplementary Figure 1).

rtACS

rtACS was applied with a noninvasive stimulation device (EBS Technologies, Kleinmachnow, Germany) certified for...
clinical use. This device generated weak current of sinus and square pulses combined in trains with frequencies ranging from 5 to 30 Hz.\textsuperscript{10–14,17} The current intensities used for stimulation were always below 500 μA (Figure 1B).

Four active stimulation electrodes were placed at or near the right and left eyeballs (transorbital) with eyes closed (Figure 1A). The return electrode was positioned at the occipital pole. Pulse shape was either square (n = 11) or sinus (n = 13). Both eyes were treated, irrespective of their lesion status (i.e., including the intact eyes). The stimulating electrodes delivered current trains during one cycle with one active channel at a time and intervals of 1 second between cycles. The number of pulses in trains was increased from two to nine pulses during the 10-day treatment course. Each session consisted of 200 to 250 cycles with five to seven 1-minute breaks.

Current thresholds were determined every day during the 10-day treatment period for both eyes at a frequency of 5 Hz. Current intensity was then increased stepwise (by 10 μA per second) starting with 0 μA. Current thresholds were defined as the value of the electrical current that elicited the first subjectively perceived flickering light, i.e., electrically evoked phosphene anywhere in the visual field with eyes closed. The point in time when the patient started to perceive clear phosphenes and/or skin sensations was defined as the “individual current threshold.” In case patients did not perceive phosphenes during rtACS (one patient in each the sham and rtACS group) the current threshold was defined as the intensity when patients perceived a cutaneous sensation. Current amplitudes for stimulation were slightly above the individual current threshold.

Stimulation frequencies were between the individual α-range (minimum) obtained from background EEG recordings at baseline and the flicker fusion frequency (maximum) that was measured daily before the stimulation session. During each session different frequencies were applied within this specified range. Flicker fusion frequency of phosphenes was determined by stepwise increasing the frequency (1-5 Hz per second). Throughout the 10-day treatment course, current amplitude and frequencies were individually adjusted to maintain phosphene perception. Therefore, stimulation parameters varied between patients and between sessions in the same patient. Figure 1B shows the stimulation parameters (current amplitudes and frequency of pulses) during the treatment course.

Sham-stimulation procedure and blinding

Although all patients and diagnostic examiners were unaware of the treatment modality, the attending physician administering the treatment was aware of the group identity. To optimize blinding of the patients and keeping the expectation level comparable between groups, a clicking sound was presented to the rtACS- and sham-group and both groups were subjected to the same electrode montage setup, except that sham stimulation patients received no current stimulation. This left sham stimulation patients with the impression that treatment may have occurred. In addition, before each treatment session a phosphenes threshold determination was conducted for each of the four stimulation electrodes in all patients. Thus, all sham patients (except one who perceived only cutaneous sensations) also experienced phosphenes (all patients learned that phosphenes may occur during electric stimulation from the patient information sheet).

Patients were only informed to which group they belonged after the final diagnostic session was completed. No sham patient was perfectly sure that he or she belonged to the sham group. All sham stimulation patients were then offered, and accepted, subsequent rtACS. All diagnostic evaluations were carried out in a blinded fashion, i.e., the examiner (study nurse) was unaware of the treatment regimen.

Patient reported outcomes

Vision-related quality of life: NEI-VFQ: The NEI-VFQ was originally designed to measure the dimensions of self-reported vision-related QoL in subjects who suffer from chronic eye diseases.\textsuperscript{19–21} In this study the validated German 39-item version of the NEI-VFQ was used.\textsuperscript{21} It measures the influence of visual disability and visual symptoms on different health domains. Considering that vision-related QoL is multidimensional, the NEI-VFQ consists of 39 rating items in 12 subscales: general health (two items), general vision (two items), ocular pain (two items), difficulties with near vision activities (six items), difficulties with distance vision activities (six items), limitations in social functioning because of vision (three items), mental health symptoms because of vision problems (five items), role difficulties because of vision problems (four items), dependency on others because of vision problems (four items), driving problems (three items), color vision problems (one item), and peripheral vision problems (one item). By averaging the vision-related dimensions, except general health, a composite score was generated that ranged from 0 (“worst possible functioning”) to 100 (“best possible functioning”). Although the NEI-VFQ assesses ordinal patient ratings, averaged subscale and total instrument scores were generated as suggested in the revised manual by the developer of the NEI-VFQ.\textsuperscript{35}

Post minus pre analyses of change after rtACS and sham stimulation were focused on the subscales general vision, general health and the NEI-VFQ composite score.

Health-related QoL: SF-36: The Medical Outcome Study Short-Form 36 Health Survey (SF-36) is a standard instrument for the assessment of general health-related QoL.\textsuperscript{23} This questionnaire was used to quantify health-related QoL in patients, independent of their actual state of health or their age. The questionnaire consists of 36 items subdivided into eight dimensions of subjective health: physical
Figure 1  (A) Left: Positioning of the stimulating electrodes. Right: Four stimulating electrodes placed at the orbit delivered current trains during one cycle with one active channel at a time and two to nine pulses per train. The number of pulses per train was increased during the 10-day treatment course (day 1 = 2/3, day 2 = 4, day 3 = 5, day 4 = 7, day 5 = 8, day 6 = 8, day 7 = 9, day 8 = 9, day 9 = 9, day 10 = 9). The total number of pulses applied to patients varied between 56,000 and 71,000. Each session contained of 200 to 250 cycles interrupted by five to seven 1-minute pauses between. During each session different frequencies were applied. Intervals between pulses were regular within a cycle but varied between cycles. Note, that the EEG cap was not worn during stimulation. (B) Stimulation parameters during the 10-day rtACS treatment course separately for patients with square versus sinus pulses (M ± SD). The mean current amplitude was slightly lower in patients treated with sinus pulses (240.4 ± 120.0) than square (250.1 ± 94.9), T = 0.11, P = 0.915. The mean stimulation frequencies (Hz) were significantly lower in patients with square (17.0 ± 2.7) compared with sinus (22.9 ± 3.0), T = −5.68, P < 0.001.
functioning (10 items), role limitations because of physical problems (four items), bodily pain (two items), general health perceptions (five items), vitality (four items), social functioning (two items), role limitations because of emotional problems (three items), and emotional well-being (five items). All items can be combined to form two summary scales: the physical component score and the mental component score. Component scores were generated by adding the item responses and including given loadings for the different dimensions. Subscale and component scores ranged from 0 (“worst possible functioning”) to 100 (“best possible functioning”).

In addition, there is one single item (self-reported health transition) that is not part of the eight dimensions and the component scores. This transition item queries the subjective change of health status and is scored from 1 (enhanced) to 5 (declined). In the current study, the German translation of the SF-36 was self-administered and patients were asked to rate the items based on the experiences during the last 4 weeks.23

For an optimal measurement of QoL in visually impaired persons, it is reasonable to use both questionnaires, the SF-36 for general health status and the NEI-VFQ for vision-targeted questions.19,22

QoL questionnaires were sent to all patients by envelope through the regular mail because answering self-administered questionnaires at home is known to result in more realistic estimates than questionnaires completed in interviews or while the investigator is present.36 Although the NEI-VFQ was returned by all patients included in the current study, the SF-36 was answered by only 12 sham and 21 rtACS patients.

Visual field diagnostics

The visual field defect was assessed with a campimetric method, the computer-based high-resolution perimetry (HRP, 16 degrees vertically × 21.5 degrees horizontally, for a detailed description see references4,25,30,31). During a single HRP test 474 light stimuli were presented in a dense grid of 19 × 25 stimulus locations. Each patient performed at least three monocular tests that were superimposed to define intact, partially damaged (relative defect) and absolute defect visual field areas (Figure 1). “White” spots indicate intact regions where all stimuli were detected. Defective visual field sectors are either “grey” areas of relative impairment where stimulus detections are inconsistent, or “black” areas where no stimuli were detected at all indicating absolute defect visual field areas. The number of detected fixation controls and false-positive responses were recorded to assure sufficient reliability.

Figure 2 shows an overlap of campimetric HRP results of all damaged eyes separately for the left and the right eye in both groups.

Static and kinetic monocular visual fields were measured with a Twinfield perimeter (Oculus, Lynnwood, WA). A fast threshold strategy was used to determine threshold values at 66 positions of the 30-degree visual field. Target stimuli (size: III/4 mm², color: white, luminance: 318 cd/m²/0 db, duration: 0.2 second) were presented on a background with constant luminance of 10 cd/m². Test positions where no stimulus was detected even when presented with maximum luminance were recorded as absolute defects. Test positions with stimulus detection at elevated luminance above the expected physiologic value were recorded as relative defects. The foveal threshold and the mean threshold of all tested 66 positions were recorded for subsequent analyses.

Further, visual field size was assessed by 24 meridians (spaced by 15 degrees) in kinetic perimetry. Targets with constant luminance of 0 dB moved from the periphery toward the center of the visual field at a constant velocity of 2 degrees per second. Patients were asked to press a button on target detection and the mean eccentricity of detected targets in degrees of visual angle was analyzed.

Visual acuity and contrast vision

Visual acuity and contrast vision were measured monocularly with best possible corrected refraction. Snellen test charts were presented at a distance of 6 m for distance vision and a Landoldt-ring test at a distance of 40 cm for near vision. Contrast sensitivity was measured with Oculus test charts.

Outcome measures

The primary outcome measure was the percentage change from baseline of detection ability (DA) in defective visual field sectors (relative and absolute defect) as observed by HRP visual field tests. To calculate DA change after treatment the baseline value of the endpoint “percentage of hits within the defective visual field” was used as a reference point (= 100%).

Secondary outcome measures were DA change in the total HRP visual field test (including both defective and intact visual field), DA change in near-threshold perimetry (foveal threshold and mean threshold of the total visual field in dB), eccentricity change in kinetic perimetry (mean eccentricity of visual field borders in degrees of visual angle), and reaction time change in computer-based HRP. Further, reliability parameters of HRP (fixation accuracy and false-positive results) were analyzed.

Statistical analyses

Between-group comparisons of baseline results in primary and secondary outcome measures were made using a two-tailed t test because there was no stratified randomization. The NEI-VFQ subscale scores were calculated according to the guidelines of the NEI-VFQ manual. Between-group
comparisons for PROMs at baseline were calculated with the Mann-Whitney U test for unpaired samples.

Post-intervention and baseline results of primary and secondary outcome measures were compared by one-tailed t tests separately within the rtACS and sham stimulation group and mean post- minus pre-differences (MD) are reported. MD values were compared between groups with one-tailed t tests.

Post-intervention and baseline results of PROMs were compared with the Wilcoxon test for paired samples and presentation of results was focused on NEI-VFQ subscales general vision, general health, and the NEI-VFQ composite score. Mean post-minus pre-differences for all NEI-VFQ and SF-36 subscales (MD) are reported. Between-group differences of MD for PROMs were calculated with the Mann-Whitney U test for unpaired samples.

In patients with binocular vision impairments DA of both eyes were averaged for subsequent correlation analyses. In patients with monocular impairment only, the results of the defective eye were considered. Kendall correlation analyses were performed for post- minus pre-differences of the NEI-VFQ subscales general vision, general health, and the NEI-VFQ composite score and the percentage change from baseline of DA in HRP after rtACS and sham stimulation, respectively.

Patients of the rtACS-group were subdivided based on the criterion of DA change in defective visual field: one subgroup included patients with DA increase larger than 20% above baseline and the other subgroup with DA increase from 0 to 20%. These two groups were then compared with respect to post-minus pre-differences of all NEI-VFQ (focus on subscales general vision, general health, and the composite score) and SF-36 subscales by Mann-Whitney U test for unpaired samples.

Results at a 2-month follow-up and baseline results of primary outcome were compared by one-tailed t tests separately within the rtACS and sham stimulation group and mean follow-up minus pre-differences (MD) are reported.
MD values were compared between groups with one-tailed t tests.

Significant results are marked with *P < 0.05, **P < 0.01, and ***P < 0.001. Statistical analyses were carried out with SPSS 17.0.

Results

Group comparison for NEI-VFQ and SF-36 subscale scores at baseline

The distribution of baseline NEI-VFQ subscale scores of the rtACS and sham group are shown in Figure 3. There were no differences between NEI-VFQ subscale scores at baseline between both groups (Supplemental Table 1 for M ± SD). Concerning the SF-36 most subscales had similar scores without significant differences between rtACS and sham group (Supplemental Table 1 for M ± SD). Bodily pain was more pronounced in the sham group (60.4 ± 26.7) than in rtACS patients (84.1 ± 29.2, Z = −2.59, P < 0.01), and this was reflected in the SF-36 physical component score that was also significantly lower in the sham (45.2 ± 9.6) compared with the rtACS group (51.2 ± 8.4, Z = −2.41, P < 0.05).

Because the patient data were pooled from two clinical studies which differed slightly in their stimulation protocol (square pulse versus sinus AC waves) it was determined whether PROM results at baseline were different between the two studies but we found no significant differences between rtACS patients treated with sinus versus square pulses, except for the following trends. For the scales NEI-VFQ role difficulties (sinus: 52.4 ± 26.5 versus square: 71.3 ± 25.9) and SF-36 role limitations because of physical problems (sinus: 63.5 ± 37.7 versus square: 87.5 ± 35.4) there was a trend for better scores in the square group at baseline (Z = −1.72, P = 0.086 and Z = −1.81, P = 0.070). We also observed that NEI-VFQ scores of patients with monocular damage (n = 14) were significantly better than in patients with binocular damage (n = 28) for most subscales, except NEI-VFQ general health, ocular pain, and peripheral vision.

Group comparison for clinical outcome measures at baseline

Table 1 shows the group comparison of the ophthalmologic baseline diagnostics. There were no differences between the rtACS and the sham group at baseline for the primary outcome measure DA and for most of the secondary outcome measures (Table 1). Near vision and contrast vision were slightly better in the rtACS group at baseline. Again, there were no differences between rtACS patients treated with sinus versus square pulses for most outcome measurements. Only mean threshold in the whole visual field was significantly higher in the rtACS group treated with square pulses (9.2 ± 6.9 dB) than with sinus (4.9 ± 3.5), T = 2.37, P < 0.05).

Baseline versus post-treatment comparison for patient reported outcomes

Box- and barplot of post- minus pre-differences were calculated for the NEI-VFQ subscales general health and general vision and the NEI-VFQ composite score (Figure 4). MD for NEI-VFQ general health (Z = −0.42, P = 0.338) and the NEI-VFQ composite score (Z = −1.07, P = 0.143) did not differ between groups. Significant improvements in NEI-VFQ general vision were observed in both groups and were significantly larger in the rtACS group (MD = 11.3 ± 13.5, Z = −3.21, P < 0.001) than in the sham group (MD = 4.2 ± 9.4, Z = −1.73, P < 0.05), the between group difference being Z = −1.71, P < 0.05.

Post-minus pre-differences for all NEI-VFQ and SF-36 subscales are listed in Supplementary Table 2. Significant differences between both groups were also observed for NEI-VFQ distance activities (sham: MD = −2.3 ± 8.6; rtACS: MD = 2.9 ± 10.0, Z = −2.02, P < 0.05), NEI-VFQ social functioning (sham: MD = −0.9 ± 5.6; rtACS: MD = 2.8 ± 11.0, Z = −1.85, P < 0.05), and a trend for NEI-VFQ peripheral vision (sham: MD = −1.5 ± 13.9; rtACS: MD = 4.2 ± 9.5, Z = −1.47, P = 0.072).

There were significant post minus pre increases in the rtACS group for SF-36 social functioning (MD = 9.4 ± 21.4,


Table 1  Baseline measurements for the rtACS versus sham stimulation group

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<tr>
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<th>Sham stimulation (n = 30)</th>
<th>rtACS (n = 40)</th>
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<tr>
<td><strong>Computer campimetry</strong></td>
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<tr>
<td>Absolute detection accuracy (DA, %) in the defective visual field sectors</td>
<td>32.3 ± 22.0</td>
<td>25.4 ± 17.7</td>
<td>0.155</td>
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<td>Absolute detection accuracy (DA, %, whole tested visual field)</td>
<td>45.3 ± 29.5</td>
<td>40.5 ± 27.5</td>
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<td>Fixation accuracy (%)</td>
<td>81.2 ± 26.3</td>
<td>81.5 ± 28.7</td>
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<td>False-positive results (%)</td>
<td>5.5 ± 9.2</td>
<td>3.3 ± 5.4</td>
<td>0.208</td>
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<tr>
<td>Reaction time (ms)</td>
<td>521.7 ± 131.0</td>
<td>549.3 ± 102.2</td>
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<td><strong>Automated static perimetry</strong></td>
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<tr>
<td>Foveal threshold (dB)</td>
<td>16.5 ± 9.3</td>
<td>14.7 ± 9.5</td>
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<tr>
<td>Mean threshold (whole visual field) (dB)</td>
<td>9.0 ± 6.1</td>
<td>6.7 ± 5.6</td>
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<td>No. of absolute defects</td>
<td>27.1 ± 23.2</td>
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<td>No. of relative defects</td>
<td>14.8 ± 9.5</td>
<td>17.8 ± 12.0</td>
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<td><strong>Automated kinetic perimetry</strong></td>
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<tr>
<td>Mean eccentricity (°)</td>
<td>40.3 ± 19.4</td>
<td>38.3 ± 15.7</td>
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<td><strong>Visual acuity</strong></td>
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<td>Far vision</td>
<td>0.3 ± 0.3</td>
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<td>Near vision</td>
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<td>Contrast vision</td>
<td>9.4 ± 9.8</td>
<td>18.2 ± 22.8</td>
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DA = detection accuracy; n = eyes. Only damaged eyes (n = 70) were analyzed. Eyes with DA of more than 90% in the whole tested visual field were excluded from the analyses and considered as intact. T-values show between group differences with two-tailed significance tests.

P < 0.05, SF-36 emotional role limitations (MD = 20.0 ± 34.9, P < 0.01), SF-36 mental health (MD = 6.5 ± 12.1, P < 0.05), as well as the mental component score (MD = 6.14 ± 7.06, P < 0.01). In the sham group, none of these SF-36 scales improved and significant between group differences were observed for SF-36 emotional role limitations (Z = −1.96, P < 0.05), and the mental component score (Z = −2.24, P < 0.05). However, there was a slight but significant decrease for the physical component score in the rtACS group (MD = −2.9 ± 6.9, P < 0.05).

Comparing rtACS patients treated with sinus versus square pulses significantly better scores were observed in the square-pulse subgroup for NEI-VFQ distance activity (sinus: −2.1 ± 8.6 versus square: 5.7 ± 10.6; Z = −2.28, P < 0.05) and NEI-VFQ composite score (sinus: −0.02 ± 6.3 versus square: 6.6 ± 6.6; Z = −2.12, P < 0.05). This was confirmed by a trend of better scores in the square pulse group for further NEI-VFQ scales, namely, general vision (sinus: 6.7 ± 12.7 versus square: 16.4 ± 13.1; Z = −1.8, P = 0.066) and NEI-VFQ social functioning (sinus: −3.2 ± 10.5 versus square: 6.8 ± 11.2; Z = −1.9, P = 0.053). There were no differences between patients with monocular versus binocular damage regarding PROMs.

Baseline versus post-treatment comparison of primary and secondary outcome measures of vision performance

Figure 4  Post- minus pre- differences of NEI-VFQ scores
general health, general vision, and the NEI-VFQ composite score in the rtACS and sham group (M ± SE). NEI-VFQ General health (Z = −0.42) and the NEI-VFQ composite score (Z = −1.07) did not differ between groups. Improvements in NEI-VFQ General vision (Z = −1.71) were significantly larger in the rtACS group.

The percent change from baseline of DA was calculated (1) in defective visual field sectors, i.e., the section of the visual field where improvements of visual function was expected (primary outcome measure), and (2) in the whole tested campimetric visual field, i.e., including intact regions. For both measures the improvement was significantly larger in the rtACS group than in the sham stimulation group (Figure 5). There was a trend for better DA performance after rtACS in younger patients (r = −0.245, P = 0.096).

Although there was a significant difference between groups for DA change in defective visual field sectors (Figure 5), the absolute DA change was comparably high in both groups (placebo: MD = 5.9 ± 7.8, P < 0.001; rtACS: MD = 5.1 ± 6.0, P < 0.001) and did not differ between
groups (T = 0.54, P = 0.295). A larger percentage change from baseline in rtACS patients was also observed for DA in the whole tested visual field, whereas the absolute change did not differ between both groups (T = −0.71, P = 0.241; placebo: MD = 2.2 ± 4.5, P < 0.01; rtACS: MD = 3.4 ± 10.0, P < 0.05). Apparently, the values of absolute and relative DA change are closer in the sham stimulation than in the rtACS group.

There were no significant changes in reliability parameter of HRP (fixation accuracy and false-positives rate, both in %) in both groups.

In automated static perimetry the percentage change from baseline of the foveal threshold after rtACS was 3.1 ± 23.4 (T = 0.82, P = 0.208) and slightly worsened after sham stimulation (MD = −8.0 ± 28.9, T = −1.43, P = 0.082) with a significant between group difference (T = −1.71, P < 0.05) (Figure 6). The foveal threshold remained unchanged in both groups (placebo: MD = 0.7 ± 6.6, P = 0.273; rtACS: MD = 0.7 ± 3.1, P = 0.087; between group difference: T = 0.05, P = 0.482).

Concerning all tested positions in static perimetry after rtACS the defect depth was reduced in absolute terms by 0.5 ± 1.1 dB (T = 3.02, P < 0.01) and 14.5 ± 35.7 dB in relative terms, i.e., as percentage change over baseline, respectively (T = 2.51, P < 0.01). The absolute change in sham patients was not significant −0.1 ± 0.9 dB (T = −0.44, P = 0.331) and the percent change over baseline was even negative −1.4 ± 16.7 dB (T = −0.42, P = 0.340). The between group difference was significant (T = −2.38, P < 0.05).

The post minus pre absolute differences of the outer visual field borders, i.e., the change of mean eccentricity, were rather small and did not differ between both groups (T = −0.89, P = 0.189, placebo: MD = 1.6 ± 2.9, P < 0.01; rtACS: MD = 2.6 ± 6.1, P < 0.01). The percentage change of mean eccentricity revealed significantly larger visual field extensions in the rtACS group (11.8 ± 25.7 degree, T = 2.90, P < 0.01) versus 4.0 ± 16.0 degree (T = 1.24, P = 0.114) after sham stimulation (T = −1.51, P = 0.068).

Again, perimetry results indicate that the absolute and percentage change values are close to each other in sham stimulation patients, whereas the percentage change is considerably larger in the rtACS group.

Comparing rtACS patients treated with sinus versus square pulses no significant differences were observed between groups concerning primary and secondary parameters of vision performance.

**Association of patient reported outcome measures and post-intervention change of vision performance**

Comparing patients with small or no increases of DA (0-20%, n = 12) with those showing larger increase, i.e., above 20% (n = 10), improvements in NEI-VFQ general health (Z = −2.24, P < 0.05) and general vision (Z = −2.45, P < 0.01) were significantly larger in rtACS treated patients that had DA gains >20% (Figure 7). The NEI-VFQ composite score (Z = −1.25, P = 0.106) did not differ between groups. Supplementary Table 3 lists post- minus pre-differences of all NEI-VFQ and SF-36 subscales separately for rtACS treated patients that experienced 0-20% versus > 20% DA improvement.

Increased subjective functioning was associated with visual field improvements, i.e., relative DA change in defective visual field sectors (Supplementary Figure 2). However, the association between post- minus pre-differences for NEI-VFQ general health, general vision, and the composite score with the primary outcome measure was weak to modest in both the sham and the rtACS group. No significant correlations were observed between SF-36 post- minus pre-differences and DA change.

**Stability of vision improvement at a 2-month follow-up**

Visual field improvements (primary outcome) in the rtACS group were still present at a 2-month follow-up: the relative DA change in % in defective visual field compared between follow-up and baseline was 31.6 ± 105.9 (T = 1.86,
That is about 10% less than at the final diagnostics immediately after rtACS as shown in Figure 5. In the sham group, the difference was 4.8 ± 3.7 which was not significant. Because of the high interindividual variability, the between group difference did not reach significance at follow-up (T = −0.92, P = 0.181). Concerning the whole visual field the relative DA change in % was 19.9 ± 102.2 (T = 1.22, P = 0.116) in the rtACS group and −5.3 ± 32.1 in the sham group. Again, the between group difference did not reach significance (T = −0.87, P = 0.194).

Discussion

The aim of the study was to examine whether stimulus detection performance in computer based visual field tests (HRP) increased after rtACS in patients with optic nerve damage and if this was associated with changes in self-reported vision- and health-related QoL. Two PROM questionnaires were used to assess QoL: the vision-specific NEI-VFQ and the generic SF-36.

The success of QoL and PROM studies depends to a great extent on the choice of appropriate instruments. They must be selected according to the domains they measure and the populations and pathologies for which they are designed. Unfortunately, there is no disease-specific questionnaire that assesses vision-related QoL in neuroophthalmologic patients. The NEI-VFQ was chosen for the current study because it is capable of reflecting impairments in cerebrally damaged patients with visual field defects although it was specifically designed for ophthalmic patients. A German version of the neuroophthalmologic supplement to the NEI-VFQ was recently developed but was not yet available for the current study.

The rtACS and sham group at baseline showed highly comparable visual functioning as measured by both primary and secondary outcome measures as well as PROM (Table 1, Supplementary Table 1, Figure 3). For this reason, comparison of change after intervention between both groups was justified. However, we cannot fully exclude that the age difference may have affected the outcome. There was a trend toward statistical significance of the correlation with the primary outcome measure, i.e., younger patients tended to improve more from the therapy (r = −0.245, P = 0.096). All correlations with patient reported outcome measures were below 0.2 and not significant, except for NEI-VFQ peripheral vision. Again, greater subjective improvements of peripheral vision tended to be associated with younger age (r = −0.329, P = 0.073).

Change of primary (Figure 5) and secondary outcome measures (Figure 6) as well as PROM (Figure 4), when taken alone, showed a rather uniform picture of improved visual functioning after rtACS and, with some exceptions, no such improvements were seen in the sham stimulation condition. To determine whether stimulation-induced vision improvements were associated with increased vision-related QoL, the rtACS group was split into two groups: those patients having experienced relative DA increases in the defective visual field sectors of smaller than versus those with greater than 20%. As expected, patients with DA increase >20% had also more pronounced improvements of self-reported visual functioning (NEI-VFQ subscale scale general vision).

Furthermore, changes in the primary outcome measure were correlated with PROM change (NEI-VFQ general health, general vision, and composite score). The correlations were only weak indicating that there are high levels of unexplained variance when correlating subjective questionnaire results with psychophysiologic parameters, in this case visual field measures. Although this can be in part explained by the fact that optic nerve damage associated visual field loss is asymmetric or only on one eye, this
observation supports the previously reported mismatch of objective (perimetric) and subjective measures of vision: visual field enlargements after (behavioral) visual field training are not always associated with subjective improvements and, vice versa, subjective improvement occurred even in the absence of visual field size changes.\(^{39}\) We speculated that factors other than visual field size, such as temporal processing and attention, contribute to the subjective vision.

Finally, some NEI-VFQ scales were sensitive to changes in visual field size improvements after rtACS. Of particular interest is the subscale “general vision” that not only improved by more than 10 points in the rtACS group but also significantly differed from the sham group with an increase of about 4 points. Considering only rtACS-treated patients, there was a significant difference of almost 10 points between patients with larger vision improvements in computer-based perimetry (>20% DA increase) compared with patients with DA increases <20%. As we previously reported, between groups differences that exceed 10 points can be considered as clinically relevant based on the NEI-VFQ developers’ experience.\(^{5,19}\)

These findings indicate that not only objective visual field parameters (such as detection in perimetry) should be measured in interventional studies, but the assessment of vision-related QoL provides a meaningful and valuable subjective complement to objective visual field data. Because the correlation of both was modest at best, the subjective and objective approaches to assess visual loss seem to represent different aspects of vision. This emphasizes the need to obtain both kinds of measurements to fully appreciate the patients’ individual situation. Another advantage of using PROM assessment by the NEI-VFQ (ideally including the neuroophthalmologic supplement) is that this may help to weigh the risks and benefits (ratio of effort/cost) of interventions.

Our results also show that rtACS treatment is capable of modifying the adult visual system function after damage in a noninvasive manner. Most recently, it was observed that trains of alternating current produce phosphenes in a frequency-dependent manner indicating that visual cortex is activated.\(^{40-42}\) Zaehle et al.\(^{43}\) reported that application of alternating current within the individual alpha frequency range over the visual cortex of 10 healthy subjects elevated the alpha power measured at parieto-central electrodes, even at current levels that did not provoke phosphene perceptions. Increased individual alpha power was shown to be relevant for enhancing cognitive performance also in other studies.\(^{44,45}\)

The mechanisms leading to improved vision after noninvasive rtACS still have to be clarified. We propose that visual field enlargements in patients with visual field defects through rtACS are due to increased neuronal synchronization. Within this context a recent study by Logothetis et al.\(^{46}\) is of interest showing that effects of electrical microstimulation may be different from visual stimulation. Electrical microstimulation of the lateral geniculate nucleus (LGN) in monkeys increased activation only in cortical areas receiving monosynaptic connections from LGN, whereas extrastriate areas were suppressed. A possible reason for this effect may be linked to the temporal structure of the electrical stimulation, which is different from activity evoked by visual stimuli, and results in inhibition of local cortical circuits. This finding cannot be easily translated to the situation of noninvasive rtACS. We also do not yet know if rtACS has effects on the retina only or also directly alters the primary visual cortex or higher cortical areas. Logothetis et al. used local microstimulation, exciting probably only a small fraction of LGN neurons that evoked focal activity in primary visual cortex. We suggest that in case of rtACS much larger numbers of retinal and LGN cells are stimulated, thus eliciting synchronous and coherent oscillatory activity spreading over cortical areas with long-term after effects.

We have shown that improved vision after rtACS has a functional relevance in patients’ everyday life. Noninvasive current stimulation may thus have a clinical potential for the treatment of visual impairments. The ubiquitous ability of plasticity in the adult visual system may be due to the considerable residual vision capacity of the deafferented visual cortex.\(^{47}\) However, it should be kept in mind that even after effective intervention, QoL of patients with visual field loss is still at a reduced level. Though visual functioning can be improved for both, clinical parameters and PROM, the remaining visual field defect still leaves the patients with subjective impairments that require continued attention (treatment).

A methodologic limitation of the study is the blinding procedure. We cannot fully exclude that sham patients might have had different feelings about the treatment’s efficacy since they experienced phosphenes or cutaneous sensations only at the very beginning of each session during 3-5 minutes (session duration maximal 40 minutes). However, none of the sham patients was certain if he or she belonged to the sham group.

In the current study we did not ignore the long noticed need for a NEI-VFQ scoring algorithm different to the conversion into interval scales.\(^{48,49}\) We still decided to adopt the more traditional method of building 12 subscales and a composite score.\(^{19,20}\) Thus, a limitation of the study could be the assumption that averaging patient ratings would not yield true measurements. Therefore, attempts were made to calibrate vision-related QoL questionnaires with item response models or Rasch analysis.\(^{49}\) It is obvious that the NEI-VFQ does not have an acceptable subscale structure when subscales are built the traditional way. One also has to question the content validity of the subscales, especially those of “scales” that consist of only one item.

In the current study the traditional way of building subscales was therefore chosen to allow for a comparison with another study where NEI-VFQ results were measured.
after visual field training in brain-damaged patients. In that study significant increases in subjective vision-related QoL were observed in a larger number of NEI-VFQ subscales following training (eight of 12 versus four of 12 in the current study). In contrast to the current study, the subscale “general vision” improved by only about three points in the training study ($P < 0.1$) and the subscale “driving problems” had the worst score before visual field training and improved by more than 10 points. Subjective driving impairments did not improve in the optic neuroptahies patient sample of the presented study. A possible reason for this finding may be the different topographies of visual field loss in the patient samples of both studies. Although the majority of patients with optic neuropathy were still allowed to drive, most patients with postchiasmatic visual field loss after stroke were told by their attending physician to discontinue driving, which markedly reduces life satisfaction. Consequently, treatment induced changes are much more noticeable by and relevant to postchiasmatic patients.

A further limitation of the current study is that some reconceptualization of self-estimated functioning may have taken place in the course of the treatment, i.e., a response shift. This implies that at two different time points a person might give different answers in a questionnaire or measurement as for instance the QoL questionnaire NEI-VFQ, either because of “real” changes in the QoL as a result of external factors such as a treatment or a change in health status or because the subject might have changed his or her perception about health and QoL. However, we suppose that because of the short treatment period of only 10 days it is unlikely that a change of internal standards occurred on which individual judgements were based. Thus, we consider it unlikely that some reconceptualization of the underlying construct of vision-related QoL has occurred. More probably response shift may have occurred in patients of our previous behavioral study because visual field training was carried out for a longer period of at least 6 months.

**Conclusion**

The current study is the first that systematically assessed QoL before and after noninvasive brain current stimulation as a therapeutic option for patients with visual field defects. The findings generally confirm previous observations of subjective improvements after visual field training but the nonbehavioral and short procedure of noninvasive current stimulation avoids the metodologic problems of the training studies. rtACS is clinically also more practicable because it is much shorter (10 days) than behavioral training (180 days). In sum, our study validates the value of QoL tools to document the dynamics of visual field functions after brain lesions and confirms the efficacy of rtACS. Changes of health- and especially vision-related QoL should be addressed on a routine basis in future studies since pre- and post-QoL measurement will enhance the understanding of the clinical relevance of functional improvements after interventions such as rtACS. This adds another important dimension to clinical assessment that is closer to the patients’ subjective visual state than traditional perimetric procedures alone.

Finally, our study presents class 1b evidence that noninvasive brain stimulation with alternating current is a viable approach to induce vision restoration and improvements in QoL.

**Acknowledgments**

We thank Romualda Michalik, Sandra Heinrich, and Nicole Mäther for their patient care and performing diagnostic measurements as well as for their technical and administrative assistance.

**Supplementary data**

Supplementary data related to this article can be found online at doi:10.1016/j.brsc.2011.07.003.

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