Non-invasive electric current stimulation for restoration of vision after unilateral occipital stroke☆☆★

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A B S T R A C T

Occipital stroke often leads to visual field loss, for which no effective treatment exists. Little is known about the potential of non-invasive electric current stimulation to ameliorate visual functions in patients suffering from unilateral occipital stroke. One reason is the traditional thinking that visual field loss after brain lesions is permanent. Since evidence is available documenting vision restoration by means of vision training or non-invasive electric current stimulation future studies should also consider investigating recovery processes after visual cortical strokes. Here, protocols of repetitive transorbital alternating current stimulation (rtACS) and transcranial direct current stimulation (tDCS) are presented and the European consortium for restoration of vision (REVIS) is introduced. Within the consortium different stimulation approaches will be applied to patients with unilateral occipital strokes resulting in homonymous hemianopic visual field defects. The aim of the study is to evaluate effects of current stimulation of the brain on vision parameters, vision-related quality of life, and physiological parameters that allow concluding about the mechanisms of vision restoration. These include EEG-spectra and coherence measures, and visual evoked potentials. The design of stimulation protocols involves an appropriate sham-stimulation condition and sufficient follow-up periods to test whether the effects are stable. This is the first application of non-invasive current stimulation for vision rehabilitation in stroke-related visual field deficits. Positive results of the trials could have far-reaching implications for clinical practice. The ability of non-invasive electrical current brain stimulation to modulate the activity of neuronal networks may have implications for stroke rehabilitation also in the visual domain.

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1. Introduction

Each year, approximately 16.9 million people worldwide suffer from first stroke [1]. Many stroke survivors experience various forms of visual impairment, including eye movement disorders, perceptual deficits, and, most commonly, visual field defects [2]. Visual field defects arising as a consequence of posterior strokes typically occur on one side of the visual field in both eyes, a condition called homonymous hemianopia (HH). Stroke affecting the occipital lobe is the most common cause of HH, constituting 70% of all cases [3]. However, HH may not be complete but involve only a quarter of the visual field (quadrantanopia) or resemble a scotoma. Also heterogeneous perceptual and neuropsychological deficits may accompany posterior lobe damage and HH [4] even in the ipsilesional “intact” field [5]. Patients may not be conscious of the visual field defects, or may not attribute their symptoms to HH [6]. HH often has major consequences, including difficulties in reading, performing visual search and driving [7]. Various activities of daily living and mobility may also be impaired, and rehabilitation of other stroke symptoms hindered [8]. The presence of HH has been shown to significantly affect patients’ quality of life (QoL) [9].
In the hyperacute phase of ischemic posterior stroke, perfusion can be restored by means of intravenous thrombolytic treatment (tPA) which has been successful in reversing HH, however, tPA is only indicated when the neuronal tissue is not yet permanently damaged by the ischemia [10–12]. Since patients presenting with a single symptom of HH are classified by the National Institutes of Health Stroke Scale (NIHSS) as supposedly only “mild” deficits, tPA is not administered judging that the risk of hemorrhage outweighs the benefits [11]. After the tissue damage has developed, spontaneous recovery is unpredictable and often incomplete, occurring mostly within the first weeks after stroke onset and being unlikely past 6 months [10,13]. Beyond the limited early, spontaneous recovery phase, post-stroke visual field defects are considered rather permanent [13].

In the post-acute phase, there is some evidence supporting the usefulness of compensatory scanning training and visual restoration training (VRT) for patients with HH after stroke to improve vision [14,15]. However, HH is still considered to lead to permanent disability in most patients. Hence, discovering a successful treatment for chronic stroke-related HH would be pivotal. Future studies are needed to determine the potential of non-invasive current stimulation to ameliorate post-stroke visual field defects in this underserved patient group. The research network “Restoration of Vision after Stroke” (REVIS) consists of four European research centers from Germany, Finland, Italy and Poland and a commercial partner (NeuroConn, Illmenau, Germany) (funded by 2012 ERA-NET NEURON program). The aim of REVIS is to better understand the neuronal mechanisms of brain plasticity after visual field loss (HH) and to find appropriate protocols to restore vision in stroke patients using non-invasive brain stimulation.

1.1. Plasticity of the visual system

Some recovery of vision can be achieved even beyond spontaneous recovery many years after the damage using training with visual stimulation paradigms at the visual field borders [15–18] or deep in the blind field [19,20]. Following visual field training, changes in the location and magnitude of the visually-induced BOLD signal have been demonstrated, providing support for the idea of underlying plastic mechanisms [21,22].

Patients with visual cortical damage often demonstrate preserved residual vision [23] that constitutes the basis for enhancing visual functions in brain-damaged visually impaired patients even many years after the lesion [15]. In addition to residual capacities at the cortical site of damage, vision recovery in patients with extensive unilateral damage of V1 may involve activation of extrageniculate and/or extrastriate pathways [21].

1.2. Electrical stimulation to reduce vision deficits: current evidence

Repetitive transorbital alternating current stimulation (rtACS) involves non-constant current applied transorbitally [24]. Ten days of rtACS treatment have been shown to reduce visual deficits associated with prechiasmatic visual pathway injury as judged by enlargement of visual fields, improvements in visual acuity, reduced reaction times, and enhanced vision-related QoL measures [25–27]. The proposed mechanism is improved synchronization of neuronal networks firing, likely also involving residual areas surviving the injury. This is compatible with the observation that ACS applied over occipital cortex of healthy subjects modulates oscillatory brain activity as demonstrated by entrainment in the alpha band after stimulation [28]. Moreover, similar increases in alpha power have been observed to occur after rtACS in patients with visual field loss due to optic neuropathy [27,29]. Finally, functional connectivity was strengthened in response to rtACS in patients, and perceptual improvements were found to correlate with such functional connectivity changes [30]. By inducing a “re-learned synchronization response”, rtACS is hypothesized to enhance visual function after damage to various parts of the visual pathway [31]. A most recent study indicated that ACS in the alpha range strengthened the alpha band in general and thus may be promising in brain disorders involving abnormal neural synchronization [32].

In contrast to transcranial direct current stimulation (tDCS), rtACS is an underinvestigated field especially with respect to clinical applications. The potential of rtACS in the treatment of occipital strokes remains to be elucidated.

Application of tDCS alters cortical function by modulation of the impact of spontaneous activity due to excitability changes [33] leading to alterations in intracellular cAMP levels and calcium influxes [34,35]. Generally, given a sufficiently long stimulation duration and adequate stimulation intensity, anodal stimulation increases neuronal excitability, while cathodal tDCS reduces it [36].

In healthy subjects, tDCS applied over visual areas induces changes in contrast and motion sensitivity, improves detection sensitivity of targets in a visual discrimination task, and modifies the amplitude of visual evoked potentials [37–39]. Lang et al. [40] demonstrated a decrease in the phosphene threshold following anodal tDCS over the visual cortex, which was reversed by repetitive TMS which is known to modulate effects of electrical stimulation on visual perception. In contrast, cathodal tDCS was found to increase the phosphene threshold transiently [40].

In HH-patients, the combination of occipital anodal tDCS applied centrally to the Oz position with computer-based visual field training of light detection appears to enhance visual functional outcomes compared to training without tDCS [41], suggesting that anodal tDCS may have a positive impact on vision restoration. However, this study did not consider the possible mechanisms of action.

1.3. Electrical stimulation to reduce vision deficits via rebalancing hemispheric activity

After damage due to stroke, remaining (residual) function at the lesion site is negatively influenced by the relative hyperactivity of the intact hemisphere resulting in an above-normal inhibitory modulation of the lesioned hemisphere [42,43]. In fact, when the lesioned hemisphere exerts less inhibitory inputs on the damaged hemisphere resulting in even more inhibition of the lesioned hemisphere, it may be an unfavorable situation for recovery to apply an excitatory stimulation centrally over the visual cortex which was done in the Plow et al. study [41]. We therefore suggest making use of lateralized anode and cathode positions considering whether the cortical structures that are targeted are intact or affected by the stroke. Thus, tDCS protocols should be designed to focus on the modulation of the above-mentioned cortical imbalance between excitation and inhibition. Based on these considerations, three basic tDCS protocols could be used to re-achieve balance after unilateral stroke (Fig. 1): (1) cathodal tDCS over the intact hemisphere to reduce inhibition of the damaged hemisphere, (2) anodal tDCS over the damaged hemisphere to enhance excitability and (3) simultaneous stimulation with cathodal tDCS over the intact cortex and anodal tDCS over the impaired cortex in a dual mode setting.

Recently, in a study involving subjects with visual neglect, it was shown that after dual-mode tDCS, i.e., anodal tDCS over the right posterior parietal cortex (PPC) and cathodal tDCS over the left PPC, reduced symptoms were observed in the line bisection task [44]. On the other hand, anodal stimulation with a central placement of the anode was found to reduce intracortical inhibition in healthy subjects [45]. Thus, it appears necessary to also compare central anodal stimulation over visual cortex with lateralized positioning of the electrodes in single-mode and dual-mode settings. Based on these considerations the following stimulation protocols were developed for the REVIS trial.
**2. Methods**

2.1. Stimulation protocols

2.1.1. Transorbital alternating current stimulation and cathodal stimulation of the intact hemisphere

Non-invasive brain stimulation will be conducted with a battery-driven stimulator (NeuroConn GmbH, Ilmenau, Germany) through conductive-rubber electrodes placed in saline-soaked sponges. The center of the AC stimulation electrode (5 × 7 cm) will be positioned at Fpz according to 10–20-system for EEG-recordings. The reference electrode (10 × 10 cm) will be placed on the right upper arm. In the active-rtACS condition stimulation is given for 20 min daily with a maximum of 1.5 mA, i.e. well above the phosphene threshold. Stimulation starts with a 5 Hz burst and then frequency increases in step of 1 Hz up to 30 Hz, what constitutes an “rtACS block” with duration of 48 s. These blocks are repeated until the stimulation time of 20 min is reached.

In the active-tDCS condition, tDCS is given immediately before rtACS for 10 min with 1 mA via one electrode placed at either O1 or O2 position (cathode, 3 × 3 cm) above the intact hemisphere with the anode at Fpz. The impedance will be kept below 10 kΩ.

2.1.2. Bilateral dual-mode direct current stimulation over visual cortex


tDCS will be delivered using two 5 × 5 cm² saline-soaked sponge electrodes connected to a battery driven stimulator (NeuroConn GmbH, Ilmenau, Germany). Electrodes for tDCS will be placed in O1 and O2 position according to 10–20-system. The stimulating anode electrode will be placed over the injured occipital pole (cathode placed supraorbitally either Fp1 or Fp2), while the stimulating cathode electrode will be placed over the spared one (anode placed supraorbitally either Fp1 or Fp2). This electrode configuration was chosen to simultaneously enhance the excitability of the impaired occipital cortex and to decrease the excitability of the intact hemisphere. The impedance will be kept below 10 kΩ. tDCS will be delivered with fixed amplitude for 20 min per day (2 mA, 30 s fade-in).

2.2. Challenges related to the design of the sham conditions

Experimental blinding with respect to active or sham-conditions will be ensured by using the same electrode montage and stimulation duration for all participants in one study center. Concerning rtACS, the design of the sham-condition is crucial to reach the best possible blinding of the patients with respect to the treatment arm, as participants must be informed that rtACS can cause phosphenes [46]. The rtACS-sham condition is designed in a way that only occasional current bursts are given to create short but therapeutically ineffective phosphenes. This sham-condition (one 5 Hz burst/min with individual amplitude for phosphate perception) proved to be useful in a previous study since none of the study participants was able to tell for sure to which study arm they belonged.

tDCS elicits cutaneous sensations that progressively diminish and disappear at the beginning of the session because of habituation. Therefore, in the tDCS sham condition, current will be ramped up for 30 s, then stopped and at the end of the session ramped down for another 30 s. In this way we will elicit a comparable extent and duration of cutaneous sensations in both groups of patients (real and sham tDCS).

2.3. Safety aspects of the applied electrical current stimulation

Due to the relatively large surface area of the stimulating electrodes, current densities will not be higher than those in other studies. The maximum current density will be 42 μA/cm² below AC stimulating electrodes and 15 μA/cm² below the reference electrode. In the cathodal paradigm it is 111 μA/cm² below the DC stimulating electrodes and 80 μA/cm² in the bilateral anodal–cathodal paradigm. This corresponds to a total charge density lower than 0.1 C/cm² which is below the safety limits established for non-invasive brain stimulation [47]. Safety guidelines for direct current application to the human brain were reported [47,48].

No serious adverse effects, such as epileptic phenomena or evidence of neural tissue damage, have been reported with either form of
stimulation. Perception of phosphenes is often encountered during rtACS, and, occasionally, has also been reported to occur between rtACS stimulation sessions [27]. Other minor effects occasionally reported to occur during stimulation or treatment periods with rtACS or tDcS have included skin irritation and short-lasting sensations such as tingling or itching on the scalp beneath the electrodes, sleep disturbances, mild headache, and fatigue [27–29,46–51]. The following undesirable events will be asked for immediately after each stimulation session and at the following day prior to the next stimulation session: headache, dizziness, fatigue/drowsiness, skin sensation, blurred vision immediately after stimulation, and others (open question). These records will finally allow us to establish whether potential benefits of the stimulation outweigh potential risks.

2.4. Study design

The treatment period comprises two weeks excluding weekends with daily stimulation (20–30 min) while keeping stimulation parameters constant. Fig. 2 depicts the study design of clinical studies. In Finland, a 2-arm efficacy and safety study will be conducted comparing (1) active-rtACS with (2) sham-stimulation (n = 20 in each group). Thus, a protocol is used which is already known to improve visual fields after optic nerve damage [27]. In Germany, HH-patients are treated with tDcS and rtACS in a sequential order to investigate whether preceding cathodal tDcS over the intact hemisphere may enhance rtACS effects in hemianopic patients compared to sham-stimulation and rtACS without preceding tDcS. In a 3-arm study the following groups are contrasted: (1) sham—tDcS/active-rtACS (n = 15), and (2) active-tDcS/active-rtACS (n = 15) compared to (3) sham—tDcS/sham—rtACS. Here, cathodal tDcS will be used to inhibit the visual cortex of the intact hemisphere, with the aim to reduce the interhemispheric imbalance. In Italy, a 2-arm tDcS-study (n = 15 in each group) will apply anodal (excitatory) tDcS over the damaged hemisphere combined with cathodal (inhibitory) tDcS over the intact hemisphere, which will be compared to sham-stimulation. All sham patients will be offered to receive stimulation treatment after the final follow-up evaluation. Concerning the sample sizes there is no data available which may be used to perform a sample size calculation.

2.5. Inclusion and exclusion criteria

Inclusion criteria are (1) HH due to ischemic or hemorrhagic stroke, (2) age between 18 and 75 years, (3) lesion age at least 6 months, (4) stable visual field defect across baseline measurement (subjects with spontaneous fluctuations and recovery of vision excluded), (5) presence of residual vision and detectable gradual transition between the intact and the absolutely blind part of the visual field according to evaluation of the clinician, (6) best corrected visual acuity at least 0.4 (20/50 Snellen) or better.

Exclusion criteria are (1) known active malignancy, (2) eye or central nervous system diseases that interfere with the study (including poorly controlled glaucoma), (3) electric or electronic implants (e.g. heart pacemaker), (4) metal artifacts in the eyes or head (with the exception of dental prosthesis or shunts), (5) expected low compliance (e.g. in case of known psychiatric disease, known drug abuse, and dementia syndromes), (6) epileptic seizure within the last 10 years, and (7) use of antiepileptic or sedative drugs.

2.6. Description of the randomization procedure and ethical approval

The randomization of patients into real stimulation and sham groups will be done by employees who do not have contact with study participants, using dedicated randomization software (http://www.statsol.de/). The randomization information is then provided to the experimenter who performs the stimulation. A specific study mode will not be used.

Study participants as well as diagnostic staff will be masked with regard to the group allocation until follow-up diagnostics 8 weeks after end of treatment (Fig. 2). Stratified block randomization of patients in verum and sham groups is carried out at the Institute of Medical Psychology Magdeburg centrally for all study centers. The stratification considers the severity of the defect (mean detection threshold in perimetry as a result of visual field testing at baseline, 2 levels) as a potential prognostic factor.

The REVIS studies have been approved by local ethics committees in the three study centers (University of Magdeburg, Medical Faculty, Magdeburg/Germany; no. 173/13; Hospital District of Helsinki and

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**Fig. 2. Study design:** REAL* stimulation groups are either i) rtACS or rtACS combined with transcranial tDcS (Germany), ii) rtACS (Finland), and iii) combination of anodal (excitatory) tDcS stimulation on the damaged hemisphere together with cathodal (inhibitory) tDcS on the intact hemisphere (Italy). All sham patients will be offered to receive stimulation treatment after the final evaluation.
Uusimaa Ethics Committee; no. 49/13/03/01/13), (IRCCS S. Raffaele Pisana, Roma no. 4/13/20/05/13). The studies will be conducted in accordance with the Declaration of Helsinki in its current version, the guidelines of the International Conference on Harmonization of Good Clinical Practice (ICH-GCP), and the applicable national legislation. All participants are required to give written informed consent. Since patients participate in the study when they are already in the chronic stage the study procedures do not interfere with receiving a standard therapy.

2.7. Study endpoints and analysis plan

Outcome parameters are summarized in Table 1. An electronic case report form is used to document the study results for each participant.

2.7.1. Visual field change as the primary outcome measure

The primary outcome parameter is visual field change, i.e., mean threshold in standard static perimetry and improvement in detection accuracy in high-resolution perimetry (HRP). The mean threshold in standard static perimetry is obtained as an average value indicating an approximation of light detection sensitivity of near-threshold stimuli. In contrast, detection accuracy in HRP corresponds to the ability of the subjects to detect above-threshold light stimuli. During HRP, small static white dots (duration: 150 ms) are presented clearly above threshold in a randomized sequence at 474 different positions in a 25 × 19 grid on a dark screen.

Both visual field parameters are considered equally important and are therefore defined as primary outcome measures. The treatment effect of at least one parameter must be significant compared to sham. It is hypothesized that rtACS and rtACS combined with cathodal tDCS induce significant visual field change when compared to sham-stimulation. Similarly, we expect visual field improvements after dual-mode tDCS when compared to sham.

The basis of the analysis is the results of the initial, final and 2-month follow-up diagnostic of the patients participating in the study. In order to perform between group comparisons the relative change (%) over BASELINE will be determined at POST and at FOLLOW-UP (see Fig. 2) for each endpoint as 100*(POST resp. FOLLOW-UP – BASELINE)/BASELINE. Primary analysis is performed with Friedman ANOVA and Dunnett comparisons with the sham group.

Because the primary outcome measure is identical between all three centers, we will then be able to establish which non-invasive current stimulation method (1. rtACS alone, 2. rtACS combined with cathodal tDCS above the intact hemisphere, or 3. bilateral tDCS) is most effective in improving visual functions in stroke patients. However, this interpretation is limited by a potential “site” effect.

Secondary outcome parameters are additional parameters of visual functions derived from HRP and standard perimetry including reaction times on light stimuli presented during HRP and sensitivity thresholds for light detection within certain areas of the visual field.

Furthermore, visual acuity, contrast vision, and reading performance (International Reading Speed Texts, IREST) will be considered. Patient-reported outcomes are assessed by means of quality of life (QoL) instruments for vision-related QoL and health-related QoL. The secondary analyses will be performed with an adjustment for multiplicity.

2.7.2. Exploratory outcome measures

Visual evoked potentials (VEP), resting-EEG power spectra and connectivity measures will be obtained as exploratory outcome measures. The hypotheses concerning network-wide effects of rtACS and normalization of interhemispheric balance by tDCS will be further tested using EEG for functional connectivity (FC) analysis. FC represents dynamic, time-varying interactions between brain regions and is defined as relation (or lack of thereof) between EEG-signals recorded from two or more brain locations. Based on our initial results [30], it is expected that rtACS treatment strengthens FC in patients and affects network topology, e.g. leading to greater clustering within the visual sub-network, and that tDCS affects interhemispheric FC. Furthermore, in Finland and Germany, fMRI will be used as an additional means of studying activation patterns in response to visual stimuli and FC.

3. Summary and discussion

Understanding how to modulate synchronization within cortical networks, in the human brain, may enable current stimulation to become a potential therapy in the treatment of stroke-related vision deficits. Much less is known about the visual system compared to the motor system, e.g., [52,53]. Now the first large-scale consortium trial of non-invasive brain stimulation for vision rehabilitation after stroke is conducted. Several research problems will be addressed. Firstly, we wish to gain insights in alterations in brain networks after visual system damage, which have not been studied in detail. To this end, also neuroimaging techniques (EEG, fMRI) will be used. Patients will be compared to age-matched healthy control subjects at baseline (before start of the treatment) and brain activity/connectivity patterns will be correlated with patients’ perceptual capabilities. Moreover, application of the described single- and dual-mode tDCS protocols may provide further evidence for the role of interhemispheric connectivity in the lesioned brain.

Secondly, the REVIS study will address methodological issues related to non-invasive brain stimulation, namely the design of optimized sham-conditions. This is a challenging problem, especially when using ACS [51]. Because the number of clinical studies using non-invasive brain stimulation techniques is on the rise, this issue needs to be carefully addressed to avoid results that are difficult to interpret.

A number of questions cannot be addressed within the framework of REVIS: Any induction of clinically relevant aftereffects requires the application of sufficient long and frequently repeated stimulation periods and little is known about the minimum number of stimulation sessions that are needed to induce stimulation aftereffects on a physiological level that then relate to the enduring functional changes of visual functioning. We decided to keep the number of stimulation sessions constant within ten days. Unfortunately, it is hardly possible to perform repeated perimetry and HRP during the stimulation course since profound visual field testing is extremely time-consuming. Another limitation is that visual neglect, typically occurring after right-sided strokes, may simulate or coexist with HH, complicating diagnostics and assessment of outcome measures related to daily life activities. We cannot exclude the effect of mild neglect since neglect testing is not part of the test battery.

Finally, the overall goal of REVIS is to define evidence-based stimulation protocols for clinical use. Paradigms for modulating the synchronization within partially damaged visual networks by rtACS and tDCS are developed and evaluated with respect to safety and efficacy of different electric current stimulation protocols to improve vision in post-stroke patients with unilateral visual field loss. REVIS is the first definitive trial on non-invasive brain stimulation for stroke-patients suffering from persistent visual field loss combining approaches of rtACS and tDCS.

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Table 1

<table>
<thead>
<tr>
<th>Outcome parameters.</th>
<th>Baseline diagnostic</th>
<th>Post intervention</th>
<th>Follow-up</th>
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<tr>
<td>Clinical status</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Visual acuity and contrast</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Standard perimetry (high resolution, static and kinetic)</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Reading performance</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Quality of Life (vision-related and health-related)</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td>Resting EEG</td>
<td>x</td>
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<tr>
<td>fMRI</td>
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Note: Not all tests will be applied in each study center.
References


