Review

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Effects of Noninvasive Brain Stimulation in Cerebral Stroke Related Vision Loss

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Abstract:
Background & Aims: *Although vision loss is a very common and serious complication in cerebral stroke patients, there appears to be a mismatch in the number of studies establishing the potential of noninvasive brain stimulation modalities for post stroke vision loss compared to other complications of cerebrovascular accidents. This review aims to describe the current literature on noninvasive brain stimulation (NIBS) techniques in post cerebral stroke vision loss and suggests future considerations in this field.*
Methods: *Three independent reviewers conducted a systematic search in PUBMED database. We included all publications covering vision-loss after cerebral stroke (case reports, RCT, pilot studies). This search yielded six relevant papers that met our criteria.*
Results: *We found two case reports (1 tDCS, 1 TMS), one comparative case study (tDCS), and three randomized, controlled clinical pilot studies (all tDCS). No study applying tACS on stroke related vision loss fit our criteria. Our review shows that very few studies so far investigated non-invasive brain stimulation techniques as a treatment option in cerebral stroke related vision loss. The case reports as well as the small pilot studies;however, suggest a beneficial effect of applying tDCS over the primary visual cortex in addition to vision restoration training (VRT) in regaining parts of the visual field and accelerating the recovery time. These results are comparable and consistent with findings on stroke related motor and speech rehabilitation with the application of different NIBS protocols. A case report on repetitive TMS (1Hz) showed its potential use in down-regulation of visual cortical areas to cease visual hallucinations as a concomitant in visual field loss, also known as Charles-Bonnet-Syndrome.*
Conclusion: *Although studies are scarce and data are limited, we have found some evidence that NIBS-techniques have positive effects on the rehabilitation of visual field loss post cerebral stroke. More studies are needed to investigate mechanisms of action and proof of efficacy. systems.*

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INTRODUCTION

The incidence of cerebrovascular accidents is 9 million annually worldwide (Fisher et al., 2011) and 795,000 annually in the United States (Stroke facts, 2015). A 2013 prospective study reports a prevalence of visual field loss in 52% of patients post stroke (Rowe et al., 2013). Other sources report an incidence of 25% (Warning Signs of Stroke, 2012). Studies have shown that vision loss is responsible for a considerable reduction in quality of life in stroke patients (Gall et al., 2010) and increases the risk of falls (Langhorne et al., 2000; Davenport et al., 1996).

Post stroke visual impairment can be described as a blurring, central vision loss, diplopia, ocular movement dysfunction, visual processing dysfunction, or a partial or complete visual field loss following different patterns, depending on the size and location of the stroke along the visual pathway (see table 1) (Visual problems after stroke, 2012) (Shrestha et al., 2012). The patterns of visual field loss are shown in Figure 1.

Spontaneous recovery of vision is unlikely to occur after the first 6 months following stroke (Zhang et al., 2006). Still, there is potential to activate neural plasticity of the visual system after this period by highly specific and time- consuming training, such as Vision Restoration

Table 1. Types of post stroke visual impairment

Types of visual impairment	Most common location of stroke	Most common symptoms
Central vision loss	Retinal Stroke	Partial or complete unilateral blindness
Visual processing dysfunction	Non dominant parietal lobe stroke	Visualspatial hemineglect
Ocular movement dysfunction	Brainstem stroke, or cranial nerve III, IV, VI pathways	Diplopia, blurring, strabismus, nystagmus
Visual field loss*	Cerebral stroke in visual pathway	Peripheral visual field blindness (usually bilateral)

*Visual field loss patterns shown in Figure 1

Training (VRT) or compensatory scanning training (Pollock et al., 2011; Sabel et al., 2011; Kasten et al., 1998; Mueller et al., 2008; Poggel et al., 2004). Additionally, there is scientific evidence in animal and human studies showing neuroplastic effects of repetitive transorbital alternating current stimulation (rTACS) in the visual system after pre- chiasmatic optic nerve or retinal damage in terms of regaining neurophysiological as well behavioral functionality (Sergeeva et al., 2015; Fedorov et al., 2011, Gall et al., 2011, Sabel et al., 2011).

Noninvasive Brain Stimulation Techniques

Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation is a tool currently used in clinical research to modulate neural plasticity. Relatively weak and diffuse, constant current flows are induced via scalp electrodes to influence the polarization of the underlying neural tissue (Purpura and McMurtry, 1965; Scholfield, 1990). Several studies have shown that anodal stimulation to the cerebral cortex can increase spontaneous neural activity, whereas cathodal stimulation may lead to decreased activity (Bindman et al., 1964; Creutzfeld et al., 1962; Purpura and McMurtry, 1965). This is corroborated through neuroplastic changes such as long term potentiation (LTP) or long term depression (LTD). In many neurological conditions tDCS may have positive effects on either regaining a lost function or decreasing the severity of symptoms (Nitsche et al., 2008). Non-invasive neuromodulation in stroke rehabilitation has been proven useful as an adjuvant to well- established therapeutic techniques with regard to motor function (Triccas et al., 2015), aphasia (Otal et al., 2015; Elsner et al., 2015) or dysphagia (Pisegna et al., 2015, Yang et al., 2015).

Transcranial Alternating Current Stimulation (tACS)

In tACS the electrode montages are similar to tDCS, however the polarity (alternating anode and cathode) can be switched in different frequencies, which creates a sinusoidal waveform. Neural networks in the brain produce several rhythmic activities oscillating in a spectrum range from 0.05 HZ to 500 HZ (Reato et al., 2013). Transcranial alternating current stimulation can entrain the neural oscillations in a frequency-specific manner to improve synchronization of neuronal network firing (Gall et al., 2015). This procedure has also been applied in neuropsychiatric diseases for some decades, however the long-term plasticity remains unknown and further exploration of its clinical applications is needed (Reato et al., 2013; Battleday et al., 2014; Fregni el at. 2012).

Transcranial Magnetic Stimulation (TMS)

A more focal stimulation technique also used for cortical modulation and neuropsychiatric diseases is Transcranial Magnetic Stimulation (TMS). A coil applied on the scalp generates a magnetic field that goes through the skin and scalp and generates an electric field that can cause neuron depolarization, thus changing the occurrence of spontaneous neural activity (Boggio et at. 2006). The synaptic plasticity is again related to LTP and LTD and neuroprotective mechanisms (Chervyakov et al., 2015; Fregni et al. 2012). The pulses can be applied singly or in a repetitive manner. The frequency of pulses can have different effects: while high frequency is thought to be responsible for neural excitability and therefore increased blood flow, low frequency stimulation has inhibitory effects (Fregni et al. 2012). TMS is the only FDA approved noninvasive brain stimulation therapy to date. Repetitive TMS has been approved by the FDA for the management of treatment-resistant depression in 2008, while single pulse TMS for pain caused by migraine in 2013.

Non-invasive brain stimulation (NIBS) has been in the scope of many research areas. Although the mechanisms of action are not completely understood, NIBS is thought to influence neural plasticity by neural sprouting, synaptogenesis and neurogenesis (Brunoni et al., 2008).

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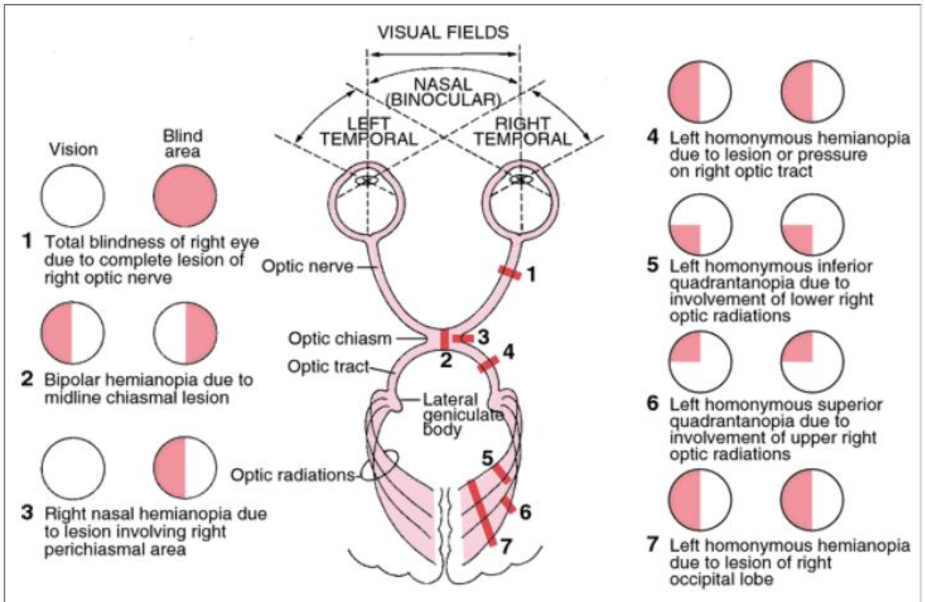

Figure 1. Patterns of Visual Field Loss according to location of the lesion. A stroke in any of the numbered locations results in the associated visual field loss. From Polaski and Tatro, 1996.

While NIBS has been applied widely in research for different clinical conditions, in the field of post-stroke vision-loss only few studies have been conducted.

Therefore, the purpose of this review is to describe the current literature to date on non-invasive brain stimulation techniques in post-cerebral stroke vision loss and to identify gaps in the literature and discuss possible considerations for future trials.

METHODS

Two reviewers performed an electronic search in PubMed database limited to studies written in English. All studies published until July 2015 were included. The selected search terms were "stroke", "transcranial direct current stimulation", "transcranial alternating current stimulation", "transcranial magnetic stimulation" and "vision disorders". Studies were included if they met the inclusion and exclusion criteria described in table 2.

Filtering the search results by title and abstract yielded nineteen papers. Upon a second review by all three authors, methodology was examined and 10 papers were excluded. A final thorough review led to three more exclusions.

Figure 2 shows a complete schematic of the review process.

Table 2. Inclusion and Exclusion Criteria

Inclusion	Exclusion
Adult subjects	Animal trials
Cerebral stroke subjects	Visual neglect
Vision loss post-stroke	Literature review
Use of non-invasive brain stimulation	
RCT, case reports, case control studies	

RESULTS

The systematic search for non-invasive brain stimulation in vision-loss after stroke yielded six studies corresponding to our inclusion and exclusion criteria. We found two case reports (1 tDCS, 1 TMS), one comparative case study (tDCS), and three randomized, controlled clinical pilot studies (all tDCS). No study applying tACS on stroke, focused specifically on vision loss, did fit our criteria. Table 3 shows the highlights of the six study protocols.

tDCS

A case report of one patient with chronic left posterior cerebral artery stroke leading to right side hemianopia, showed changes in fMRI signals as an index of cortical recovery after 2x30min of 2mA direct current anodal stimulation over Oz (cathode Cz) per day, 3 times per week over 3 months as an adjuvant to vision restoration training (VRT: for detailed description see Kasten et al., 1998) (Halko et al., 2011). One comparative case study on two patients with real and sham tDCS stimulation combined with VRT showed significant improvement of the visual field in the verum stimulation compared to sham, but only a trend to significance in the within-group comparison (Plow et al., 2011). The same research group

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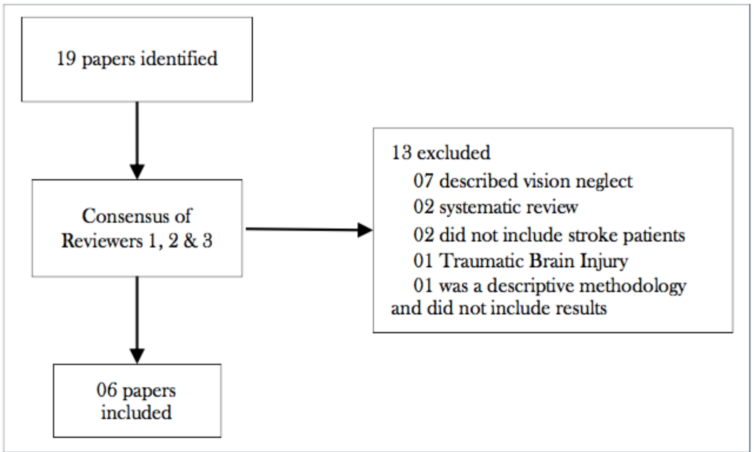

Figure 2. Review process

conducted a double-blind, f, pilot study with the same regimen of tDCS combined with VRT on twelve patients (10 stroke, 2 surgical trauma). The results confirmed the superiority of active tDCS+VRT treatment compared to sham tDCS+VRT treatment in terms of accelerating recovery processes over the period of 3 months and increasing the visual field post treatment (Plow et al., 2012a). Another cross-over, double-blind, sham-controlled study applied tDCS over the visual cortex (1,5mA, 5 sessions; anode over calcarine sulcus; cathode Cz) in twelve chronic posterior cerebral artery stroke patients with visual field loss, to examine its effect on motion detection in the unaffected hemifield (Olma et al., 2013). The results showed significant improvement in motion detection in verum stimulation even after a 14 and 28 day follow-up.

tACS

No study looking solely on stroke related vision loss and applying tACS could be found so far.

We found one clinical observational study using a transcranial alternating current stimulation protocol in stroke using the stroke severity scale (NIHSS) as primary outcome measure. Although significant improvement in overall function in treatment group was reported, with even additional improvement after 1-month follow up, detailed information and separated statistics on visual field loss could not be found (Fedorov et al. 2010).

rTMS

Only one case report fitting our inclusion and exclusion criteria could be found. In this study however, 1Hz rTMS (80%intensity) over the occipital pole was used to

investigate its effect on pseudo hallucinations as a concomitant symptom after bilateral ischemia in calacrine fissures with a resulting homonymous central scotoma. Although the hallucinations vanished after treatment, no information about the visual field loss and its recovery was given by the authors (Merabet et al., 2003).

DISCUSSION

Due to the limited amount of literature on this particular topic, the evidence of NIBS being effective in rehabilitation of vision loss in cerebral stroke is weak; however, consistent. The main technique studied in this field of research so far is tDCS, whereas rTMS was used in a case report only. Of the six publications included, only three are RCTs. The population sizes in all studies were small, therefore limiting their power. Additionally, there have been no trials, which replicated the observed effects. One pilot study showed a heterogeneous patient population where stroke and surgical trauma were mixed. The quality of the studies; however, was not assessed systematically.

Future perspective

Noninvasive brain stimulation is a thriving research field from understanding basic neural functions up to translational applications in rehabilitation medicine. As recent reviews focusing on NIBS and stroke related disorders show, there is therapeutic potential to these modalities. Many questions concerning properties of stimulation protocols are yet to be answered. Especially in the field of stroke related vision loss, more randomized controlled trials with sufficient sample size are needed. Limitations were found in the heterogeneity of subjects regarding location and size of lesion. Since visual field loss can occur with lesions in various locations along the visual pathway, different stimulation techniques might have more specific effects to those lesions. As previous studies in stroke rehabilitation suggest, the normalization of the imbalanced brain due to unilateral damage should be in the scope of stimulation protocol (Corbetta et al.,

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Table 3. Summary of Papers included in this review

Author/year	Type of study	n	Stroke type	Intervention	Stimulation Parameters	Outcome	Results
Plow et al 2012b	RCT proof-of-concept	8	Unilateral postchiasmal stroke or brain damage	tDCS + VRT	Anode: Oz Cathode: Cz 2x30 min/day, 3/week, 3 month	VF-border with HRP	tDCS+VRT shows greater expansion of VF compared to sham+VRT
Plow et al 2011	Comparative case study	2	Unilateral chronic ischemic stroke	tDCS + VRT	Anode: Oz Cathode: Cz 2x30 min/day, 3/week, 3 month	VF-border with HRP fMRI	tDCS+VRT shows greater expansion of VF compared to sham+VRT
Olma et al 2013	RCT crossover	12	Chronic occipital ischemic lesions	tDCS	Anode: Calcarine Sulcus Cathode: Cz 1.5mA, 20 min, 5 days	Motion perception	tDCS improved motion perception in intact hemifield
Halko et al 2011	Case report	1	Chronic left posterior cerebral artery stroke	tDCS + VRT	Anode: Oz Cathode: Cz 2mA, 2x30 min/day, 3/week, 3 month	Electrical field changes VF-border with HRP	Significant correlation between electrical field and change in fMRI signal consistent with tDCS facilitation, VF-border increased
Plow et al 2012a	Randomized, double-blind, clinical pilot	12	Not specified	tDCS + VRT	Anode: Oz Cathode: Cz 2mA, 2x30 min/day, 3/week, 3 month	Stimulus detection and VF-border with HRP	tDCS+VRT accelerates recovery
Merabet et al 2003	Case report	1	Cardioembolic infarction causing multiple and bilateral occipital damage	rTMS	1 day sham + 1 day active 1 Hz rTMS for 10 min, 80% stimulator output intensity striate cortex	Self report of hallucinatory experience	Suppression of hallucinations for one week

tDCS = tanscranial direct current. VRT = vision restoration training. QOL = quality of life. HRP = high resolution perimetry. VF = visual field. fMRI = functional magnetic resonance image.

2005; Olivieri et al., 1999). Therefore two basic approaches can be proposed: increasing activity in lesioned hemisphere and decreasing activity in the intact hemisphere. We found a proposed clinical trial protocol considering different montages and current settings in vision loss after unilateral occipital stroke (Gall et al., 2015).

Much like the application of NIBS in research of different clinical conditions; some modifications to the protocols need to be applied in cerebral stroke vision loss trials. These include combination of different Neuromodulation techniques, modification of treatment intensity and duration, more detailed comparisons of the optimum timing of the stimulation in relation to the stroke, and different positioning of the electrodes. Exploring these options may result in a clearer understanding of the most efficacious treatment protocol, and thus, a better understanding of the mechanism of the treatment. These exploratory studies could potentially give NIBS techniques more direct clinical relevance and increase the generalizability of the results.

CONCLUSION

In summary, very few studies thus far have investigated non-invasive brain stimulation techniques as treatment options in cerebral stroke related vision loss. The case reports as well as the small pilot studies; however, suggest a beneficial effect of applying tDCS as adjuvant to VRT to increase residual vision. These results are consistent with findings on stroke related motor and speech rehabilitation (Triccas et al., 2015; Otal et al., 2015; Elsner et al., 2015). Anodal stimulation of the Calacrine Sulcus showed improvement in motion detection. Repetitive TMS (1Hz) showed potential use in down-regulation of visual cortical areas to complete cessation of visual hallucinations as a concomitant in visual field loss, also known as Charles- Bonnet-Syndrome. This review shows that there is a lack of systematic, highly powered investigations of NIBS on cerebral stroke related visual field loss and that further studies are needed.

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