SCUOLA DI DOTTORATO

UNIVERSITÀ DEGLI STUDI DI MILANO-BICOCCA

School of Medicine and Surgery

PhD program in Neuroscience, Cycle XXX, Curriculum in Clinical Neuroscience

BRAIN STIMULATION FOR VISION RECOVERY

Surname: Matteo Name: Barbara Maria

Registration number: 774502

Supervisor: Dr. Cecilia Perin

Tutor: Prof. Carlo Ferrarese

Co-tutor: Prof. Cesare G. Cerri

Coordinator: Prof. Guido A. Cavaletti

ACADEMIC YEAR 2016/2017

Table of Contents:

Table of abbreviations:

AC	alternating current
ACS	alternating current stimulation
ADL	activities of daily living
AE	adverse event
AION	Anterior ischemic optic neuropathy
AMD	Age-related macular degeneration
tACS	transcranial alternating current stimulation
rtACS	repetitive transcranial alternating current stimulation
BCVA	best-corrected visual acuity
DA	detection accuracy
DC	direct current
tDCS	transcranial direct current stimulation
ES	electrical stimulation
tES	transcranial electrical stimulation
EEG	electroencephalogram
ERG	electroretinogram
GAS	Goal Attainment Scaling
HRP	high resolution perimetery
HH	homonymous hemianopia
fMRI	functional Magnetic Resonance Imaging
PET	Positron Emission Tomography
QOL	quality of life
RNS	Random Noise Stimulation
SAE	serious adverse event
SLO	scanning laser ophthalmoscope
TAP	Tubingen Automated Perimeter
TES	transcorneal electrical stimulation
TMS	transcranial magnetic stimulation
V1	primary visual cortex
VA	Visual acuity
VEP	Visual Evoked Potentials
VF	Visual Field

1. General Introduction

Up to 70% of stroke survivors are affected by Homonimous Hemianopia (Rowe et al., 2009; Pambakian, et al. 2005). Homonimous Heminaopia (HH) is the most frequent symptom of neurological damage affecting the retrochiasmal visual pathways: that leads to the loss of the left or right half of the visual field contralesional to the defect.

HH has many negative effects on functional abilities and activities of daily living (Han et al., 2002 Jongbloed et al., 1986): the most common problem is a diminished visuospatial exploration, which can impact on reading, mobility, and driving (Gall et al., 2009).

In many rehabilitation wards, HH is not still adequately considered. This could be ascribed to the fact that neurological impaired patients usually have comorbidity and more serious problem. Moreover, rarely their closest professionals are also expert in ophthalmology (almost all patients have some ocular problems additionally to the brain’s ones), so the situation gets difficult. Additionally, for many decades the hemianopia has been considered an untreatable pathology. Only in the 90’s the first studies on vision improvement of hemianopia following rehabilitation appeared.

Generally, HH’s rehabilitation techniques are divided into two main groups, depending on their relevant approaches:

- “compensatory”, aimed at allowing the visual images, that cannot be processed in the blind field, to be processed in the healthy visual field by means of behavioural training or instrumental assistance (Schofield & Leff, 2009)
- “restorative”, based on the concept that the primary visual cortex of adults has a certain resilience and sufficient plasticity to be able to reorganize itself after brain damage (Brodtmann et al., 2015).

Restorative Techniques used for rehabilitation of HH are designed to help the brain activate residual vision (Sabel et al., 2011) by training the patient to detect stimuli falling in their blind hemifield (Pollock et al., 1996).

There are two main kinds of restorative rehabilitation for hemianopia:

- "border training," which involves exercising vision at the edge of the damaged visual field;
- "blindsight training," based on exercising the unconscious perceptual functions deep inside the blind hemifield.

Both techniques have proven to be useful for recovery of different visual functions (Kasten & Sabel, 1995; Kasten et al., 1998; Kasten et al., 1999; Kasten et al., 2000; Sabel et al., 2000; Sabel et al., 2004; Poggel et al., 2006; Mueller et al., 2007; Jobke et al., 2009; Poggel et al., 2010; Gall et al., 2012; Sahraie et al., 2006, Sahraie et al., 2010; Sahraie et al., 2013).

Additionally, in the last decade recent studies applying non-invasive brain stimulation (NIBS) techniques has led to promising results in the case of a number of focal brain lesions (aphasia, hemiplegia, etc.) (Meinzer et al., 2016; Cha et al., 2014).

In the recovery of vision, studies on the effectiveness of NIBS techniques in vision restoration also appeared, showing to be effective on a large variety of visual problems going from retinal disease (Schatz et al., 2016), passing through the optic nerve disease (Gall et al., 2016) to the visual brain disease (Spiegel et al., 2013).

Particularly with respect to HH, these techniques have proven to be effective in the recovery of vision if in combination with training (Plow et al. 2011, Plow et al. 2012 and Arber et al. 2017). The effectiveness of brain stimulation alone in restoring HH is still unexplored.

Additionally, it is still also unexplored the effect of current stimulation on blindsight rehabilitation.

It would be interesting to deeply investigate what are the most appropriate methods to reactivate the injured tissue and/or to improve the visual performance in every-day life.

This work was divided into three phases; each phase led to write a paper and the relevant publications are reported in the three main chapter of this thesis.

1) The first phase was aimed to discover the state-of-art in HH rehabilitation by reviewing articles on the subject that describe the effects of restorative rehabilitation, whose long-term efficacy is still on debate. The review provides an

overview of all the possibilities of treating HH and evaluates what the most appropriate approach would be. Fifty-six articles, describing various techniques used to promote visual field recovery were analyzed. Although no formal meta-analysis was possible, the results of a semi-quantitative evaluation suggested that the obtained improvement in visual skills obtained is related to the type of training used: “border rehabilitation” seems to improve the detection of visual stimuli, whereas “blindsight rehabilitation” seems to improve their processing. Finally, the addition of transcranial direct current stimulation seems to enhance the effects of visual field rehabilitation. The results were published in the Journal of Vision (2016, July 1;16(9):11. doi: 10.1167/16.9.11).

2) The second phase was aimed to test if blindsight rehabilitation associated with tDCS is suitable for HH treatment. A pilot study was conducted representing the first attempt to associate the modulatory effects of tDCS over the parieto-occipital cortex to blindsight treatment in HH rehabilitation. Patients showed better scores in clinical-instrumental, functional, and ecological assessments after tDCS combined with blindsight rehabilitation rather than rehabilitation alone. In this two-case report parietal-occipital tDCS modulates the effects induced by blindsight treatment on HH. This exploratory study provides some considerations both on the effectiveness of training and on electric stimulation treatment. The paper was published in Journal of Physical Therapy Science 2017 Sep;29(9):1700-1705. doi: 10.1589/jpts.29.1700. Epub 2017 Sep 15.

3) The third phase was aimed to test the effects of alternating and direct current stimulation without training on hemianopia. In this phase, the Milan-Bicocca University collaborated with the Institute for Medical Psychology at Otto-von-Guericke University. At that time, they were involved in studying the effects of electrical stimulation on the hemianopics patients as active parts in the REVIS

(European consortium for restoration of vision) project. The design of the project was published in 2015 from Caroline Gall et al. on *Contemporary Clinical Trials* in a paper titled ″Non-invasive electric current stimulation for restoration of vision after unilateral occipital stroke”. The project aimed to investigate the effects of electric current stimulation on hemianopics people using the different stimulation techniques: the expected result was to assess the method effectiveness and which, among the techniques, the most efficient. The project contemplated that brain electrical stimulation is not associated with other treatments or training. The preliminary results of the Magdeburg group was presented, as a conference paper, at the 4th international symposium “Low Vision and Brain, 24-26 November 2017, Berlin”.

2. Project I: Visual field Restorative Rehabilitation after brain injury

2.1 Introduction

Visual field defects

One of the most frequent symptoms of neurological damage is a lesion affecting the retrochiasmal visual pathways that leads to the loss of the left or right half of the visual field of both eyes depending on whether the lesion is on the right or left side of the brain. Long known as homonymous hemianopsia (HH), the effects may vary from complete blindness to the loss of only a part of the affected hemifield. The lesion affects the visual fibres posterior to the lateral geniculate nucleus (LGN), and may involve the occipital lobe (about 40% of cases), the parietal lobe (30%), the temporal lobe (25%), or the pathway between the optic tract and the LGN (5%) (Grunda, Marsalek & Sykorova, 2013).

The most frequent cause is stroke: it is estimated that 20-57% of stroke survivors are affected by HH (Rowe et al., 2009), but this percentage increases to 70% in the case of a stroke involving the district supplied by the posterior cerebral artery (Pambakian, Currie & Kennard, 2005). Other possible causes are subarachnoid bleeding, intracerebral hematomas, cerebral traumas, tumours and, much less frequently, brain surgery, demyelinating diseases and congenital diseases (Zhang, Kedar, Lynn, Newman & Biousse, 2006). About 20-30% of all of the patients admitted to neuro-rehabilitation wards have visual field defects (Kerkhoff, Münssinger & Meier, 1994), whereas the visual acuity of patients with hemianopsia due to retrochiasmal lesions is generally not impaired (Zihl & von Cramon 1982). Furthermore, according to Kerkhoff (1999), 70% of the subjects with HH show "macular sparing": i.e. they have a preserved area of central vision whose amplitude ranges from 2° to 5° (Wang, 2003).

The World Health Organisation International Classification of Functioning, Disability and Health (ICF) [WHO, 2004] recognises three principal types of visual deficiency: deficit (related to the organ), disability or limitation of activities (related to the person), and handicap or restricted participation (related to society). Homonymous visual field deficits usually cause the last two: the absence of, or a deficiency in spatial information, reading disorders, and orientation deficits that cause affected subjects to bump into objects or have problems in finding their way; and major handicaps such as reduced participation in society, an inability to drive, a reduction in everyday activities, impaired independence, reduced social contacts, and severe reduction in the quality of life (Gall, Lucklum, Sabel & Franke, 2009).

One of the main handicaps affecting the quality of life of hemianoptic patients is the reading impairment called hemianoptic alexia (Leff & Behrmann, 2008), but the occurrence and entity of the reading disorders due to HH depend on the side of the deficit and the presence of macular sparing (Schuett, 2009).

Properties of cerebral hemianopsia: spontaneous recovery and blindsight

Spontaneous recovery is most frequently observed within three months of the event (Pouget et al., 2012), but seems to be relatively limited. It has occurred in 30-50% of the cases considered in various studies (Hier, Mondlock & Caplan, 1983; Zhang et al., 2006), and the degree of recovery greatly depends on the type and site of the lesion: for example, when HH is caused by an ischemic lesion, the recovery rate is no more than 10% (Gray et al., 1989). Furthermore, in the case of complete initial damage, recovery is greatest during the first ten days and, when the defect is incomplete, it is greatest in the first 48 hours and further recovery is minimal after 10-12 weeks (Zhang et al., 2006). Zhang et al. (2006) found that the possibility of spontaneous recovery during the first six months progressively decreases from 50-60% in the first month to 20% after six months, and then becomes zero; however, other authors (Trauzettel-Klosinski, 2010) claim that a slight subsequent improvement is possible even 8-12 months after the lesion.

Functional magnetic resonance imaging (fMRI) studies have shown that recovery is associated with reactivation of the primary visual cortex (V1) and the restored integrity of ipsilateral optic radiations (Polonara et al., 2011), but this seems to be conditioned by the strictly unilateral retinotopical representation of V1, which probably limits the degree of reorganisation possible in other more overlapping neural networks (Kerkhoff, Münssinger, Haaf, Eberle-Strauss & Stögerer, 1992).

A perimetry study by Çelebisoy M, Çelebisoy N, Bayam and Köse (2011) showed that spontaneous recovery occurs first in the peripheral areas of the inferior quadrants. Vision generally returns to the blind hemifield in a sequence beginning with the perception of light, which is followed by the perception of movement, shape and colour, and finally by stereopsis (Pambakian et al., 2005, Gray et al., 1989). It has also been reported that perceptual recovery may occur in a deformed and/or distorted manner in the regions bordering the scotoma (Dilks, Serences, Rosenau, Yantis & McCloskey, 2007).

Patients affected by HH may also have partially preserved visual perception in their blind hemifield (Weiskrantz, Harlow & Barbur, 1991), a condition known as "blindsight" that represents a sort of unconscious sensitivity: for example, they may be capable of discriminating certain attributes such as the colour and shape of tachystocopic stimuli presented in forced choice tasks (Sanders, Warrington, Marshall & Weiskrantz, 1974; Zeki & Ffytche, 1998) or of processing emotional stimuli in the absence of awareness (Pegna, Khateb, Lazeyras & Seghier, 2005; Bertini, Cecere & Làdavas, 2013). Sahraie et al. (2006) distinguished two types of blindsight: type 1 characterised by some residual visual capacity in the absence of any acknowledged awareness by the subject, and type 2 by impaired awareness (patients can have some "feeling" of the occurrence of an event without seeing it per se). The reality of blindsight has been confirmed by fMRI studies that have revealed the activation of the amygdala when stimuli with an affective content are presented in the blind hemifield (De Gelder, Vroomen, Pourtois, & Weiskrantz, 1999).

Blindsight has been interpreted in various ways: it may be related to the presence of so-called "spared islands" of functioning cortical striatal neurons, or spared axons fibers, that have survived the lesion and remain connected to the extra-striatal cortical region (Fendrich, Wessinger & Gazzaniga, 1992; Wust, Kasten & Sabel, 2002); in cases in which the striatal cortex is totally compromised (such as after surgical ablation), it may be due to the presence of connections between the extra-striatal/geniculate regions and sub-cortical structures (including the superior colliculus and the pulvinar) that reach the ipsilateral extra-striatal cortex via tecto-tectal pathways (Ffytche, Guy & Zeki, 1995).

However, despite their highly disabling nature, visual field defects often remain untreated because they are under-estimated by physicians or because the people affected spontaneously learn methods of compensation (Zhang et al., 2006). Many studies have demonstrated that hemianoptic patients tend to compensate for their loss of visual field by modifying their eye movements or concentrating more on the blind hemifield (Ishiai, Furukawa & Tsukagoshi, 1987; Pommerenke & Markowitsch, 1989). Together with the often conflicting results of the treatments described in the literature (Romano, Schulz, Kenkel & Todd, 2008; Marshall, Chmayssani, O'Brien, Handy & Greenstein, 2010), this probably explains why there is still no generally accepted method for rehabilitating people with visual field disorders.

Rehabilitation strategies

These can be divided into three broad categories:

1. Behavioural compensation, which is aimed at optimising patients' behaviour in order to improve their everyday functional performance. One example is explorative saccadic training (Roth T., Sokolov, Messias, Roth P., Weller & Trauzettel-Klosinski, 2009), a form of rehabilitation that consists of increasing patients' attention towards the blind hemifield in order to allow them to scan space more carefully.

2. Substitutive compensation which has the aim of extending or improving the quality of vision with the aid of optical aids such as prisms (Bowers, Keeney & Peli, 2014).

3. Restoration, which is intended to restore part of the visual field by means of rehabilitation (Kasten, Wüst, Behrens-Baumann & Sabel, 1998)

The first two are "compensatory" approaches aimed at allowing the visual images that cannot be processed in the blind field to be processed in the healthy visual field by means of behavioural training or instrumental assistance (Schofield & Leff, 2009). On the contrary, visual field training techniques are aimed at improve or even restoring visual function by training patients to detect stimuli in the blind hemifield and increase their overall sensitivity to them. This is done by administering reiterated stimuli in order to help the brain reactivate visual function (Pollock et al., 2011).

Although a number of comparative studies have been carried out (Mödden, Behrens, Damke, Eilers, Kastrup & Hildebrandt, 2012; Roth et al., 2009; Van der Wildt & Bergsma, 1997), there is still no consensus as to whether the compensatory or restorative approach is more efficacious in treating visual field loss due to brain injury (Goodwin, 2014; Dundon, Bertini, Làdavas, Sabel & Gall, 2015).

However, the aim of this review is not comparative but to describe the characteristics and value of restorative treatment, which is based on the concept that the primary visual cortex of adults has a certain resilience and sufficient plasticity to be able to reorganise itself after brain damage (Brodtmann, Puce, Darby & Donnan, 2015). The residual structures can be reactivated by means of repeated visual stimulation (Sabel, Henrich-Noack, Fedorov & Gall, 2011), alone or combined non-invasive brain stimulation (NIBS) (Ro & Rafal, 2006; Herpich, Melnick, Huxlin, Tadin, Agosta & Battelli, 2015), for which various methods and duration of treatment have been proposed. It is therefore interesting to consider which methods are more appropriate for reactivating injured tissue and/or improving visual performance in everyday life.

2.2 Methods

Between August 2015 and February 2016, the PubMed/Medline, PsycINFO and Web of Science databases were searched for original articles about retrospective and prospective studies using the key words “Rehabilitation” OR “Restoration” combined with “Visual Field” OR “Hemianopsia”. The search identified 1290 articles (793 from PubMed, 211 from PsycInfo, and 286 from Web of Science), to which a further 51 articles from other sources were added.

After preliminary screening of the titles in order to eliminate duplications, articles not written in English, and articles that were not pertinent to subject, 126 articles were examined on the basis of the following eligibility criteria: the articles had to describe primary scientific research (i.e. reviews, meta-analyses, state-of-the-art articles, and letters to the editor were excluded) into the visual rehabilitation of human beings with retrochiasmatic lesion, without the use of compensatory methods, and without being specific for driving. Fifty-six articles were included in the final analysis (Fig. 1).

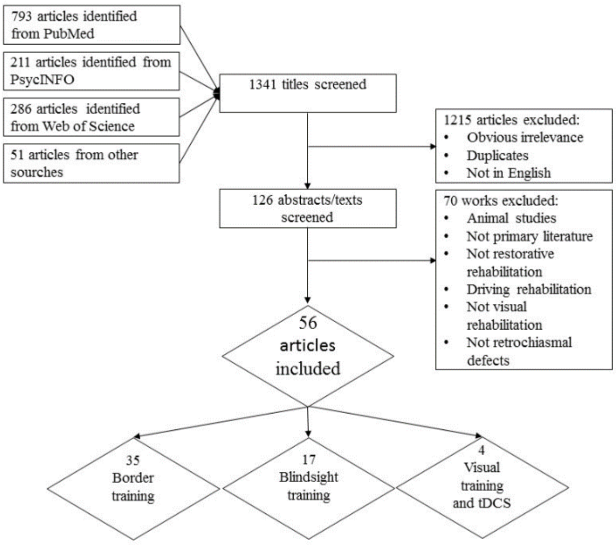


FIG. 1 - Flow chart of study selection

The articles were divided into three categories:

1) border-field training based on exercises specifically targeting the transition zone between intact and damaged visual fields (Schmielau & Wong 2007; Kasten, Wuest & Sabel, 1998);

2) blindsight training specifically targeting inside the blind hemifield (Sahraie et al., 2006);

3) rehabilitation combined with non-invasive brain stimulation techniques such as transcranial direct current stimulation (tDCS).

Each article was analysed by extrapolating the number of treated patients, the duration of the therapy, an assessment of the defect, the study end points, and the main results. Each end point of each study was associated with the type of instrument used to detect and measure it, and subsequently evaluated on the basis of the significance of the results: those that showed no positive variation in comparison with pre-training were classified as “unchanged or worsened”; those leading to an improvement that was not significant or was only described qualitatively were classified as “improved”; and those leading to a statistically significant improvement (even in only some subjects) were classified as “significantly improved”. “Improved” was also used for the studies without a statistical analysis of the results, when the results were analysed in a descriptive qualitative manner, and when the author(s) explicitly declared that there was no improvement but the presented data showed an increase in comparison with baseline.

The results were then analysed on the basis of the end point, the instrument used, and the results obtained, and the end points were then grouped into macro-categories in order to observe the effect of the rehabilitation on every general capacity related to the visual field. The first macro-category was stimulus detection, defined as the recognition of a threshold or above-threshold light stimulus. The second was stimulus processing (i.e. the ability to analyse a stimulus in time and space), defined as the perception of elements such as contrast, colour, shape, size, frequency and movement; the third included all of the neuropsychological end points such as the ability to read and be functionally attentive; and the fourth all of the subjectively/functional evaluated end points.

Two contingency tables (one for border rehabilitation and the other for blindsight rehabilitation) were drawn up in relation to each macro-category and, finally, the distribution of the results within the macro-categories were statistically analysed when the numbers allowed.

2.3 Results

Table 1 shows that 35 articles concerned border visual field rehabilitation, 17 blindsight visual field rehabilitation, and four visual field rehabilitation combined with tDCS.

TAB. 1 –Studies of Restorative Rehabilitation classified by type of treatment performed

Treatment	Code	Authors	Year	Sample size	Period of treatment
Border VFR	1	Zihl et al.	1979	12	30 one-hour sessions
	2	Zihl et al.	1985	55	80 and 120 trials daily
	3	Balliet et al.	1985	12	2-11 months
	4	Kasten et al.	1995	11 + 3	80-300 hours (1 h daily)
	5	van Der Wildt et al.	1997	1	27 one-hour sessions
	6	Kasten et al.	1998	19 + 19	6 months (150 h)
	7	Kasten et al.	2000	19 + 13	6 months (150 h)
	8	Kasten et al.	2001	16 + 6	2.3 months
	9	Julkunen et al.	2003	5	33–47 hours (1 hour 3 times a week)
	10	Mueller et al.	2003	69	6 months
	11	Poggel et al.	2004	10 + 9	6 months
	12	Sabel et al.	2004	16	6 months
	13	Reinhard et al.	2005	17	6 months
	14	Julkunen et al.	2006	1	3 months (37 hours)
	15	Kasten et al.	2006	15	3 months
	16	Schreiber et al.	2006	16	6 months (1 hour daily/6 days a week)
	17	Poggel et al.	2006	9 + 7 +7	unspecified
	18	Kasten et al.	2007	23	3 months (30 min twice daily)
	19	Mueller et al.	2007	302	6 months
	20	Schmielau et al.	2007	20	8.2 months (45 min twice weekly)
	21	Bergsma et al.	2008	3 + 6	55, 40, 40 sessions
	22	Marshall et al.	2008	6	1 month
	23	Mueller et al.	2008	17	6 and 12 months
	24	Poggel et al.	2008	19	6 months
	25	Romano et al.	2008	161	6 modules
	26	Gall et al.	2008	85	3 and 6 months
	27	Bergsma et al.	2010	11	40 hours (1 hour daily)
	28	Marshall et al.	2010	7	3 months (twice daily)
	29	Poggel et al.	2010	19	6 months
	30	Raemaekers	2011	8	10 weeks (40 hours)
	31	Gall et al.	2012	11	6 months
	32	Mödden et al.	2012	15 + 15 + 15	3 weeks (15 30-min sessions)
	33	Sabel et al.	2013	23	6 months
	34	Bergsma et al.	2014	12	13 weeks (1-hour/day – 5 days/week)
	35	Poggel et al.	2015	9	3 months
Blindsight VFR	36	Vanni et al.	2001	1	1.5 years
	37	Hyvarinen et al.	2002	1	12 and 4 months
	38	Pleger et al.	2003	3	6 months
	39	Sahraie et al.	2006	12	3 months
	40	Heriksson et al.	2007	1	5 months (twice a week)
	41	Raninen et al.	2007	2	1 year (twice a week) and more
	42	Chokron	2008	9	22 weeks
	43	Huxlin	2009	7	9–18 months
	44	Jobke et al.	2009	8 + 10	90 days + 90 days
	45	Roth et al.	2009	13 + 15	6 weeks
	46	Sahraie et al.	2010	4	50-301 sessions
	47	Bergsma et al.	2012	12	10 weeks (40 1-hour sessions)
	48	Sahraie et al.	2013	5	30 min daily/ 3 months minimum
	49	Das et al.	2014	9	≥5 day/week
	50	Vaina et al.	2014	1	11 months
	51	Elliot et al.	2015	3	4 treatment sessions
	52	Cavanaugh et al.	2015	7	≤6 months
VFR + tDCS	53	Halko et al.	2011	1	3 months (2 half-hour sessions 3 days a week)
	54	Plow et al.	2011	1 + 1	3 months (30 min / twice a day / 3 days per week)
	55	Plow et al.	2012	6 + 6	3 months (two half-hour sessions, 3 times a week)
	56	Plow et al.	2012	4 + 4	3 months (1 hour sessions 3 days a week)

Were excluded: all tDCS studies made in healthy subjects, study projects/protocols and studies that did not show results, articles that did not treat retrochiasmatic damage, rtACS sudies, the papers of Cowey et al., (2013) and Olma et al., (2013) not doing rehabilitation but “offline tDCS”.

Border field training

Border field training is the most frequently used method of rehabilitating patients with HH. The earliest approaches date back to the 1980s, when the first studies revealed an improvement in sensitivity to contrast and, above all, a post treatment increase in the visual field (Zihl & von Cramon, 1979 and 1985). Researchers have designed and tested various computer- and perimeter-based paradigms and algorithms aimed at stimulating the transition zone, each of which has its own particular characteristics, including Goldmann, Lubeck and Tubinger perimeter training, and specially designed computer programs (e.g. Vision Restorative Therapy).

The treatments themselves consist of sometimes even domiciliary sessions during which patients are asked to adopt central fixation while they are presented stimuli directed at the transition zone, the detection of which they indicate by pressing a button or key.

Table 2 shows the results of the border field rehabilitation studies.

TAB. 2 – RESULTS OF BORDER REHABILITATION STUDIES

Category – Outcome	Assessment method	No. of articles	Results			Total No. of patients
			Significantly improved	Improved	Unchanged or worsened	
DETECTION – Shift	Goldmann	7 (3, 9, 14, 20, 27, 30, 34)	1	6	0	69
DETECTION – Shift	HRP	10 (6, 8, 11, 12, 15, 19, 23, 24, 26, 29)	8	2	0	527
DETECTION – Shift	Octopus	1 (14)	0	1	0	1
DETECTION – Shift	SLO	2 (12, 13)	0	0	2	33
DETECTION – Shift	Tubinger Perimeter	4 (1, 2, 4, 21)	1	3	0	81
DETECTION – Shift	TAP	6 (6, 8, 12, 16, 18, 32)	2	4	0	105
DETECTION – Shift	Supra-threshold perimetry	1 (25)	1	0	0	161
DETECTION – Stimuli	Kinetic perimetry	1 (5)	0	1	0	1
DETECTION – Stimuli	Octopus	1 (9)	0	1	0	5
DETECTION – Stimuli	HRP	17 (4, 6, 7, 8, 10, 11, 12, 15, 17, 18, 19, 23, 24, 26, 29, 31, 35)	17	0	0	692
DETECTION – Stimuli	Microperimetry	1 (28)	1	0	0	7
DETECTION – Stimuli	TAP	4 (7, 11, 20, 24)	3	1	0	77
DETECTION – Stimuli	Supra-threshold perimetry	1 (25)	1	0	0	161
DETECTION - Misses	HRP	3 (19, 29, 31)	3	0	0	332
DETECTION - Misses	TAP	5 (6, 12, 15, 18, 24)	4	1	0	92
NPSY - Attention	HRP reaction time	8 (12, 15, 17, 19, 22, 23, 26, 35)	4	4	0	473
NPSY - Attention	Spatial attention	1 (18)	1	0	0	23
NPSY - Attention	Alertness	3 (18, 24, 32)	2	1	0	57
NPSY - Attention	Cancellation task	1 (32)	1	0	0	15
NPSY - Reading	Words per minute	3 (13, 27, 31)	3	0	0	39
NPSY - Reading	Errors	1 (32)	0	1	0	15
NPSY - Reading	Reduction in time & errors	1 (2)	1	0	0	55
FUNCT/SUBJ	Evaluation of visual field	2 (9,14)	0	2	0	6
FUNCT/SUBJ	ADL rating in Visus status questionnaire	1 (12)	1	0	0	16
FUNCT/SUBJ	ADL – Activity Daily Living interviews	1 (20)	0	1	0	20
FUNCT/SUBJ	ADL – Activities Daily Life	1 (10)	0	1	0	69
FUNCT/SUBJ	Subjective questionnaire	4 (6, 12, 13, 18)	2	2	0	75
FUNCT/SUBJ	Semi-structured Questionnaire	1 (19)	0	1	0	302
FUNCT/SUBJ	Evaluation of daily life	1 (9)	0	1	0	5
FUNCT/SUBJ	QOL	1 (26)	1	0	0	85
FUNCT/SUBJ	Barthel's ADL Index	1 (32)	1	0	0	15
FUNCT/SUBJ	Drawing Area	1 (24)	1	0	0	19
FUNCT/SUBJ	Helpfulness of rehabilitation	1 (24)	0	1	0	19
FUNCT/SUBJ	GAS	1 (34)	1	0	0	12
CORTICAL CHANGES	VEP	2 (9, 14)	0	2	0	6
CORTICAL CHANGES	PET	1 (14)	1	0	0	1
CORTICAL CHANGES	fMRI	2 (22, 30)	2	0	0	14
PROCESSING - Temporal	Temporal Resolution	1 (35)	1	0	0	9
PROCESSING - Form	Peri-Form test improvement	3 (4, 7, 8)	0	3	0	46
PROCESSING – Form	Form improvement	4 (1, 2, 20, 24)	0	4	0	106
PROCESSING – Colour	Peri-Color test improvement	3 (4, 7, 8)	2	1	0	46
PROCESSING – Colour	Colour improvement	5 (1, 2, 20, 21, 24)	0	5	0	132
PROCESSING - Frequency	Flicker recognition	2 (1, 21)	0	2	0	15
PROCESSING - Discrimination	Visual acuity	2 (18, 20, 24)	0	1	2	62
PROCESSING - Discrimination	Contrast sensitivity	2 (1, 24)	0	1	1	31
EYE MOVEMENTS	Visual conjunction search	1 (32)	0	1	0	15
EYE MOVEMENTS	Saccades	1 (15)	0	0	1	15
EYE MOVEMENTS	Search field test	1 (24)	1	0	0	19

NPSY= Neuropsychology, FUNCT/SUBJ = Functional/Subjective Evaluation, HRP= High-resolution Perimeter, SLO= scanning laser ophthalmoscope, TAP= Tubingen Automated Perimeter, QOL= quality of life, GAS= Goal Attainment Scaling, ADL= activities of daily living, VEP= Visual Evoked Potentials, PET= Positron Emission Tomography, fMRI= Functional Magnetic Resonance Imaging.

The three parameters relating to the effects of treatment on stimulus detection were border shift (DETECTION – Shift), the stimuli detection rate (DETECTION – Stimuli) and the number of missed stimuli (DETECTION – Misses). The treatment had a significant effect in terms of border shift in 13 of the 31 studies, which was mainly revealed by means high-resolution perimetry (HRP) and Tubinger perimeter, whereas the stimuli detection rate and number of missed stimuli improved in all of the studies, and significantly improved in 29.

All of the considered neuropsychological parameters (e.g. performance on the alertness, attention and cancellation tasks, and reading time and errors) showed statistically significant improvements overall: attention (tested in a total of 568 patients) significantly improved in eight out of thirteen studies, and reading abilities (tested in a total of 109 patients) significantly improved in four out of five studies.

All of the studies that analysed stimulus processing (the identification of shapes, colours temporal and flickers) found albeit non-significant improvements in 15 out of 17 results considered, but there was little or no improvement in visual acuity, contrast sensitivity or eye movement functions.

Sixteen studies measured subjective improvements in various ways (drawings of the perceived visual field, questionnaires and interviews, evaluations of daily life, visual confidence, and the helpfulness of rehabilitation), all recorded an improvement, and seven a significant improvement.

In relation to cortical function, two studies measured visual evoked potentials (VEPs), one of which obtained the appearance of a previously absent P100. Positron emission tomography (PET) revealed statistically significant diffuse changes in a single case, and fMRI revealed significant changes in a total of 14 patients participating in two studies.

The sample sizes of the border rehabilitation studies have varied widely: the largest carried out so far are those of Mueller, Mast and Sabel in 2007 (302 patients) and Romano et al., in 2008 (161 patients); the others have been decidedly smaller, sometimes considering just a single case. Treatment duration have also varied widely from just a few weeks to more than one year, but it seems that better results are obtained using at least twice- or thrice-weekly sessions for six months or more (Mueller, Gall, Kasten, & Sabel 2008).

The analyses made three months (Julkunen, Tenovuo, Jääskeläinen & Hämäläinen, 2003), six months (Schmielau & Wong, 2007), 6-12 months (Kasten & Sabel, 1995), and up to two years after the end of treatment (Kasten, Müller-Oehring & Sabel, 2001) show that the improvements persisted in most of the patients, with some differences between them. Kasten, Müller-Oehring and Sabel (2001) also claimed that age and gender had no effect on the stability of the improvements.

Finally, Schmielau (2007) suggested that binocular training is more efficacious than monocular training.

Blindsight training

Blindsight training consists of training the blind hemifield (Zihl & Werth, 1984) by repeatedly stimulating the inside of the scotoma. The method of stimulation in the various studies is very different in terms of the part of the hemifield stimulated and the stimulation protocols. Some authors stimulated the inside of the scotoma at different degrees of eccentricity, whereas others used perimetry to decide the point to stimulate before rehabilitation: consequently the depth of the scotoma involved in the different studies was different. Furthermore, the stimulation paradigms may have been dynamic or static and at different frequencies, and included flicker stimulation, pointing at visual targets, letter recognition and identification, visual comparisons of the two hemifields, grating discrimination, spiral-like stimuli, and target movements.

Table 3 shows the results of the blindsight rehabilitation studies.

TAB. 3 – RESULTS OF BLINDSIGHT REABILITATION STUDIES

Category - Outcome	Assessment method	No. of studies	Results			Total No. of patients
			Significantly improved	Improved	Unchanged or worsened	
DETECTION - Misses	Humphrey: Undetected target	1 (42)	1	0	0	9
DETECTION – Stimuli	Humphrey: Change in sensitivity	3 (39, 43, 48)	1	1	1	24
DETECTION – Stimuli	Goldmann	2 (37, 41)	0	1	1	3
DETECTION – Stimuli	HRP	1 (44)	1	0	0	18
FIELD SIZE	Goldmann	2 (36, 47)	0	1	1	13
FIELD SIZE	TAP	1 (45)	0	0	1	13
FIELD SIZE	Octopus	1 (51)	0	1	0	3
CORTICAL CHANGES	ECSG	1 (47)	0	1	0	12
CORTICAL CHANGES	MEG	2 (36, 40)	0	2	0	2
CORTICAL CHANGES	fMRI	3 (38, 40, 50)	1	2	0	5
CORTICAL CHANGES	Evoked fields	1 (41)	0	1	0	2
FUNCT/SUBJ	NEI-VFQ	1 (44)	0	1	0	18
PROCESSING – Form/Colour	Form and colour perception	1 (47)	1	0	0	12
PROCESSING - Form/Colour/Pattern	Figures, pattern and colour recognition	1 (38)	0	1	0	3
PROCESSING – Static	Verbal and motor target localisation	1 (42)	1	0	0	9
PROCESSING – Static	Letter identification	1 (42)	1	0	0	9
PROCESSING – Static	Static sensitivity	1 (51)	0	1	0	3
PROCESSING – Static	Static discrimination	1 (49)	0	1	0	9
PROCESSING – Frequency	Flicker sensitivity	3 (37, 41, 51)	0	3	0	6
PROCESSING – Frequency	Letter recognition	2 (37, 41)	0	2	0	3
PROCESSING – Frequency	Awareness	1 (48)	1	0	0	5
PROCESSING – Frequency	Gabor patch detection	3 (39, 46, 48)	3	0	0	21
PROCESSING - Motion	Simple motion	1 (43)	1	0	0	7
PROCESSING - Motion	Complex motion	3 (43, 49, 52)	3	0	0	23
PROCESSING - Motion	Motion awareness	1 (43)	0	1	0	7
EYE MOVEMENTS	Search and fixation	1 (45)	0	0	1	13
NPSY - Reading	Reading speed	1 (47)	1	0	0	12

NPSY= Neuropsychology, FUNCT/SUBJ = Functional/Subjective Evaluation, HRP= High-resolution Perimeter, TAP= Tubingen Automated Perimeter, ECSG= estimated cortical surface gain, MEG= magnetoencephalography, fMRI= Functional Magnetic Resonance Imaging, NEI-VFQ= National Eye Institute Visual Function Questionnaire.

The detection of visual field test stimuli has been evaluated in six studies involving a total of 45 patients: two found a statistically significant difference, two a non-significant difference, and two no improvement. One study of nine patients found a statistically significant reduction in missed stimuli.

Two of the four studies of visual field size obtained positive results, but only nine of the 29 patients showed greater visual field size.

Two studies of stimulus processing (Form/Colour/Pattern) involving a total of 15 patients obtained positive results. Static perception improved in four studies, and significantly improved in two. The frequency processing improved in nine studies, and significantly improved in four: one of which showed a significant improvement in reported awareness.

The results of motion perception tasks were significant in three studies involving a total of 23 subjects, one of which recorded an improvement in motion awareness.

The analyses of cortical function revealed ECSG, MEG and evoked field changes in four works. Three studies used fMRI to monitor cortical changes in a total of five patients observed an improvement.

None of the blindsight rehabilitation studies had a sample size of more than 20 subjects.

The reviewed studies highlight the fact that recovery can be slow and may require a large number of training sessions over a period of up to 18 months (Huxlin et al., 2009), although this can be reduced by using positive feedback (Sahraie, Macleod, Trevethan, Robson, Olson, Callaghan & Yip, 2010).

Transcranial direct current stimulation (tDCS)

It is believed that anodic tDCS combined with visual field training is capable of accelerating the recovery of stimuli detection, and that its effect on visual recovery is task specific: i.e. related to the rehabilitation strategy used (Plow, Obretenova, Jackson & Merabet, 2012). The effects of anodal tDCS on perimetry in healthy subjects was studied by Costa et al., (2015), Kraft et al., (2010), and Olma, Kraft, Roehmel, Irlbacher and Brandt, (2011): these Authors found an improvement in the sensitivity linked to eccentricity of the visual field and recommended the use of tDCS in HH rehabilitation.

Table 4 shows the results of the studies of combined treatment, all of which combined tDCS with border rehabilitation.

TAB. 4 – RESULTS OF VISUAL REHABILITATION AND TDCS STUDIES

Category - Outcome	Assessment method	No. of studies	Results			Total No. of patients
			Significantly improved	Improved	Unchanged or worsened	
DETECTION – Shift	HRP	3 (54, 55, 56)	2	1	0	22
DETECTION – Stimuli	HRP	2 (55, 56)	2	0	0	20
FUNCT/SUBJ	Functional questionnaires	1 (54)	0	1	0	2
FUNCT/SUBJ	ADLs	1 (56)	1	0	0	8
FUNCT/SUBJ	QOL	1 (56)	0	0	1	8
CORTICAL CHANGES	fMRI association activity	2 (53, 54)	1	1	0	3
PROCESSING	Contrast sensitivity and MNREAD	1 (55)	0	0	1	12

NPSY= Neuropsychology, FUNCT/SUBJ = Functional/Subjective Evaluation, HRP= High-resolution Perimeter, ADLs= vision-related activities of daily living, QOL= quality of life, fMRI= Funtional Magnetic Resonance Imaging, MNREAD= Minnesota Low-Vision Reading Test.

Shift stimulus detection was measured using the visual field test in three studies, two of which found a statistically significant improvement. The same two studies found also an improvement in the detection rate.

Two single-case studies observed fMRI improvements.

Three end points have been used to test functional/subjective improvements, two which revealed improvement, but little or no improvement was observed in the quality of life.

No or little improvement was found of contrast sensitivity and reading performance, too.

The use of tDCS may enhance the inherent mechanisms of plasticity associated with training: it improves the detection of stimuli in as little as one month, and broadening of the visual field occurs after three months (Plow et al., 2012).

Analysis of the distribution of the results

As can be seen in Table 5, border rehabilitation had a higher percentage of statistically significant effects on neuropsychological and stimulus detection (visual field) end points (respectively 66.7% and 65.6%), and the majority of the stimulus processing and functional/subjective evaluation results were non-significantly positive (respectively 74% and 56.2%).

TAB. 5- Distribution of the effects of border rehabilitation by macro-category of end points

BORDER	Significantly improved	Improved	Unchanged or worsened	Total
DETECTION	42 (65.6%)	20 (31.3%)	2 (3.1%)	64 (100%)
PROCESSING	3 (13%)	17 (74%)	3 (13%)	23 (100%)
NPSY	12 (66.7%)	6 (33.3%)	0	18 (100%)
FUNCT/SUBJ	7 (43.8%)	9 (56.2%)	0	16 (100%)
CORTICAL CHANGES	3 (60%)	2 (40%)	0 (0%)	5 (100%)
EYE MOVEMENTS	1 (33.3%)	1 (33.3%)	1 (33.3%)	3 (100%)

Excluding the macro-category of functional/subjective evaluation and eyemovements (which only included two end points), Table 6 shows that blindsight rehabilitation had a higher percentage of statistically significant effects on stimulus processing (55%), whereas the majority of the studies found no improvement in stimulus detection (36.4%).

TAB. 6 - Distribution of the effects of blindsight rehabilitation by macro-category of end points

BLINDSIGHT	Significantly improved	Improved	Unchanged or worsened	Total
DETECTION	3 (27.2%)	4 (36.4%)	4 (36.4%)	11 (100%)
PROCESSING	11 (55%)	9 (45%)	0 (0%)	20 (100%)
NPSY	1 (100%)	0 (0%)	0 (0%)	1 (100%)
FUNCT/SUBJ	0 (0%)	1 (100%)	0 (0%)	1 (100%)
CORTICAL CHANGES	1 (14.3%)	6 (85.7%)	0 (0%)	7 (100%)
EYE MOVEMENTS	0 (0%)	0 (0%)	1 (100%)	1 (100%)

Comparison of the two tables shows that the results were distributed differently. The sample sizes of the studies with end points falling in the neuropsychology, functional/subjective, cortical changes and eyemovements macro-categories are too small to allow comparisons in terms of percentages, but there were enough studies with stimulus detection and processing end points to make a statistical comparison of the types of rehabilitation using Fisher's exact test.

In the case of border rehabilitation, the difference in the distribution of the studies with end points in the categories of stimulus detection and stimulus processing was statistically significant ($p<0.0001$), and in favour of stimulus detection. In the case of blindsight rehabilitation, the difference in the distribution of the studies in the two categories was again statistically significant ($p=0.01$), but this time in favour of stimulus processing. The same was true in the case of the number of significantly improved cases.

2.4 Discussion

The efficacy of restorative rehabilitation

Over the last few years, various studies have overcome previous scepticism by demonstrating that it is possible to expand visual fields after a brain injury using specific rehabilitation techniques capable of stimulating the impaired areas (Romano et al., 2008; Sabel & Kasten, 2000; Sahraie et al., 2006; Pollock et al., 2011). However, despite the difficulty of making comparisons (see Appendix), the results seem to suggest that the visual capacities reacquired after different types of rehabilitation involve different mechanisms and, consequently, affect different visual skills, a supposition that is supported by the findings of neuroimaging studies.

Border rehabilitation prevalently seems to improve signal detection as the improvements in the majority of studies were detected by means of a visual field tests, which simply require recognition of the light. After border rehabilitation, fMRI shows a shift in receptive fields toward greater eccentricity and simultaneously visual field test shows a significant increase (Raemaekers, Bergsma, van Wezel, van der Wildt & van den Berg, 2011). Detecting the signal also requires the involvement of many attentional resources, and this leads to their greater synchrony, which may explain why neuropsychological tests reveal improved alertness, reaction times and attention, and post-rehabilitation fMRI and PET findings concordantly show widespread cortical activation. Activation of attention-related brain areas has also been observed (Marshall et al., 2008; Julkunen et al., 2006).

On the other hand, blindsight rehabilitation seems to affect signal processing, leading to a greater improvement in the detection and localisation of flickering, a target or movement that mainly seems to involve the areas involved in processing visual stimuli. After blindsight rehabilitation, fMRI reveals the selective activation of the brain areas involved in associative vision (i.e. V2 [object recognition], V3 [global movement processing], and V5 [movement recognition]), even though isolated findings (Henriksson, Raninen, Näsänen, Hyvärinen & Vanni, 2007) indicate that the information arising from both hemispheres seems to be processed more in the intact hemisphere.

Neural mechanisms of recovery

The mechanism underlying the effects of visual field training are still not completely clear. The restorative approach was developed on the basis of the idea that the cortical visual system is plastic and capable of reorganising itself after it has been damaged (Romano, 2009). Sabel, Kasten and Kreutz (1997) hypothesised that the survival of no more than 10-15% of the neurons in a damaged region may be sufficient to restore basic visual functions, and so repeated stimulation may reactivate the cortical neurons in that portion of the visual field and improve synaptic connectivity (Poggel, Kasten, Müller-Oehring, Sabel & Brandt, 2001) even if the blind field has only small, partially damaged areas of vision (Sabel et al., 2011).

Kasten, Wüst, Behrens-Baumann and Sabel (1998) hypothesised that the recovery zones are functional representations of partially spared neural structures in the visual area of the brain, which they classified as sharp (a small transition zone), medium, or fuzzy (scattered deficits). It is possible that these correspond to the visual field regions of recovery that Sabel, Kruse, Wolf and Guenther (2013) called “hot spots” (as against the “cold spots” that are held to be irremediably lost) because the probability of recovery increases when they are very near to each other (a visual angle of 5°) (Gall, Steger, Koehler & Sabel, 2013). Furthermore, Jobke, Kasten and Sabel (2009) hypothesised that stimulating extra-striatal cortical regions makes it possible to bypass the damaged striate visual cortex. In line with these hypotheses, the “bottleneck theory” postulates that effective training can be explained by a process of perceptual learning in the transition zones that is capable of increasing the flow of information to the residual structures of the central visual pathways (Kasten, Poggel & Sabel, 2000).

Sabel et al. (2011) argued that repeated stimulation synchronises neuronal firing in the same areas and, as this synchronisation requires attentional activation, it leads to synaptic plasticity. It is therefore interesting that there is fMRI evidence of cortical reorganisation (Raninen, Vanni, Hyvärinen & Näsänen, 2007; Bola, Gall, Moewes, Fedorov, Hinrichs & Sabel, 2014) and signs of neuroplasticity after both border and blindsight rehabilitation (Ajina & Kennard, 2012).

The data concerning the effect of the nature and site of the lesion on the results of rehabilitation are insufficient to allow any definite conclusions but, as Melnick, Tadin and Huxlin (2015) said, it is reasonable to believe that the type of damage may affect the likelihood of plasticity and compensation. Sahraie et al. (2010) suggests that recovery is less if the lesion extends anteriorly to the thalamus, and Schmielau and Wong (2007) argued that rehabilitation outcomes are more successful in the case of damage following a hemorrhagic stroke, but Mueller et al. (2007) found that the efficacy of rehabilitation was unrelated to etiology. It has also been found that the size of the area of residual vision is a strong predictive factor (Poggel, Kasten & Sabel, 2004; Poggel, Mueller, Kasten & Sabel, 2008; Mueller, 2007), although Romano et al., (2008) has asserted that rehabilitation is not affected by whether the visual field defect is complete or partial. Finally, it has been demonstrated that the effects of rehabilitation are not influenced by the duration of the lesion (Mueller et al., 2007; Romano et al., 2008).

Debates and developments

One frequent criticism of the use of border rehabilitation used to be that the characteristics of eye movements have not been duly considered. It was widely believed that, during visual field training, patients develop compensatory mechanisms that increase saccadic frequency and help them to concentrate on the shadow zones in their visual fields (Meienberg, Zangemeister, Rosenberg, Hoyt & Stark, 1981; Pambakian, Wooding, Patel, Morland, Kennard & Mannan, 2000), and that this may explain the reported 5° improvement in the blind hemifield (Sabel, Kenkel & Kasten, 2004; Reinhard et al., 2005). However, many authors have now monitored eye movements, and demonstrated that the post-rehabilitation improvement in visual fields is due to a real gain in sensitivity rather than compensation

(Kasten, Bunzenthal & Sabel, 2006; Mueller et al., 2007; Marshall et al., 2008; Marshall et al., 2010; Raemaekers et al., 2011; Gall & Sabel, 2012).

One current subject of debate is the cost/benefit ratio of restorative rehabilitation. de Haan, Heutink, Melis-Dankers, Tucha and Brouwer (2014) had analysed homonymous visual field defects using the components of the International Classification of Functioning, Disability, and Health (ICF), and pointed out that there is no benefit in expanding the visual field unless this is accompanied by functional gains. They underline that what is most important is whether or not there is an improvement in the activities of daily life, and recommended the more frequent use of parameters relating to "patient participation measures" when assessing outcomes. In order to ensure an improvement in patient participation, it is necessary to be sure that the rehabilitation induces major visual field changes, and Melnick et al. (2015) wonders homonymous visual field defects can ever disappear completely and this remains an open question.

Another aspect is the cost of the long and specific periods of training required for visual rehabilitation and retinotopic-specific learning. Compensatory techniques still have a certain advantage in terms of costs (Lane, Smith & Schenk, 2008), but it is to be hoped that these will be reduced as a result of further research into non-invasive brain stimulation (NIBS) which, when combined with rehabilitation, has led to promising results in the case of a number of focal brain lesions (aphasia, hemiplegia, etc.) (Meinzer, Darkow, Lindenberg & Flöel, 2016; Cha, Ji, Kim & Chang, 2014), including the study of restorative therapy and tDCS-induced modulation by Plow et al. (2012).

In conclusion, the results of our analysis indicate that the type of rehabilitation (border or blindsight) leads to different outcomes, and this opens up new perspectives in the development of rehabilitation strategies for the treatment of visual deficits due to permanent brain damage. It could be useful to define the type of effect desired before planning a rehabilitation programme and/or considering whether combining the two techniques may be more functionally successful.

Limitations

Comparing the results of different techniques may be questioned for four main reasons: 1) the difference in the number of the studies of the different types of rehabilitation; 2) the size of the study samples; 3) the absence of standardised stimulation protocols; and 4) the choice of the considered end points.

The number of studies of border rehabilitation (35+4) is much higher than the number of studies of blindsight rehabilitation (17); furthermore, although some of the studies of border rehabilitation have included a large number of patients, the evidence in favour of blindsight rehabilitation is based on much smaller samples. Thirdly, although it is true that the border rehabilitation method is standardised in many studies (VRT or similar paradigms), the techniques of blindsight rehabilitation have still not been standardised. However, our detailed analysis made using a checklist designed to evaluate the methodological quality of interventional healthcare studies (Downs & Black, 1998) did not reveal any critical weaknesses in the studies of either technique.

Other limitations are the variability of the end points considered: the massive presence of "detection" end point in border rehabilitation studies and "processing" one in blindsight rehabilitation studies might be a confounding factor and the fact many of the studies used very similar instruments of evaluation and rehabilitation, thus making it impossible to exclude a learning bias. However, it must not be forgotten that vision is a multi-faceted function involving various factors, such as attention and the perception of light, patterns, shapes, movement, and frequency, which justifies the use of different end points even though this makes comparisons more difficult.

3. Project II: Transcranial direct current stimulation (tDCS) combined with blindsight rehabilitation for the treatment of homonymous hemianopia: a report of two-cases

3.1 Introduction

Homonymous hemianopia (HH) is the result of retro-chiasmal pathway damage and is a common symptom of neurologic damage affecting 20–70% of stroke survivors (Rowe et al., 2009; Pambakian et al., 2005).

HH is characterized by a visual field impairment on the same side in both eyes due to a lesion contralateral to the defect. Vision impairments may vary from blindness of an entire hemifield to loss of only a part of the affected field. HH has many negative effects on functional abilities and the activities of daily living (Han et al., 2002 Jongbloed et al., 1986): the most common problem is diminished visuospatial exploration, which can impacts on reading, mobility, and driving (Gall et al., 2009).

In general, spontaneous recovery occurs within three months of the event; after six months, significant improvement is unlikely (Zhang et al., 2006; Trauzettel-Klosinski et al. 2010). Techniques used for rehabilitation of HH are designed to help the brain activate residual vision (Sabel et al., 2011) by training the patient to detect stimuli falling in their blind hemifield (Pollock et al., 1996). There are two main kinds of restorative rehabilitation of hemianopia: “border training,” which involves exercising vision at the edge of the damaged visual field, and “blindsight training,” which is based on exercising the unconscious perceptual functions deep inside the blind hemifield (Kasten & Sabel, 1995; Kasten et al., 1998; Kasten et al., 1999; Kasten et al., 2000; Sabel et al., 2000)

Both techniques have proven to be useful for recovery of different visual functions (Sabel et al., 2004; Poggel et al., 2006; Mueller et al., 2007; Jobke et al., 2009; Poggel et al., 2010; Gall et al., 2012)-Sahraie et al., 2006, Sahraie et al., 2010; Sahraie et al., 2013), and functional imaging studies have shown neuroplasticity and cortical reorganization following restorative rehabilitation (Julkunenet al., 2006; Marshall et al., 2007; Raemaekers et al., 2011; Henriksson et al., 2007; Vaina et al., 2014; Vanni et al., 2001; Pleger et al., 2003)

For HH, Plow et al. (2011), Plow et al. (2012) and Arber et al. (2017) reported that anodal transcranial direct current stimulation (tDCS) applied over the occipital cortex influenced border rehabilitation training, when associated treatments (tDCS + training) were compared with training alone. tDCS treatment, in fact, influenced recovery speed and entities. Studies on offline tDCS with hemianopic patients showed an improvement of motion perception in the healthy hemifield and, in one case, the increase speed of blindsight (Cowey et al., 2013; Olma et al., 2013). Although these studies documented the efficacy of tDCS in association with border rehabilitation, its effects on blindsight rehabilitation have not yet been studied. In the present study, we hypothesized a modulatory effect of tDCS when combined with blindsight rehabilitation. Therefore, we present a pilot study of blindsight rehabilitation after tDCS over the parieto-occipital cortex in two patients affected by chronic HH.

3.2 Methods

The study complies with the Declaration of Helsinki and was performed following approval by the ethics committee of University of Milan-Bicocca (date: 21/09/2016). Written informed consent was obtained from both patients. The study design was a crossover AB BA.

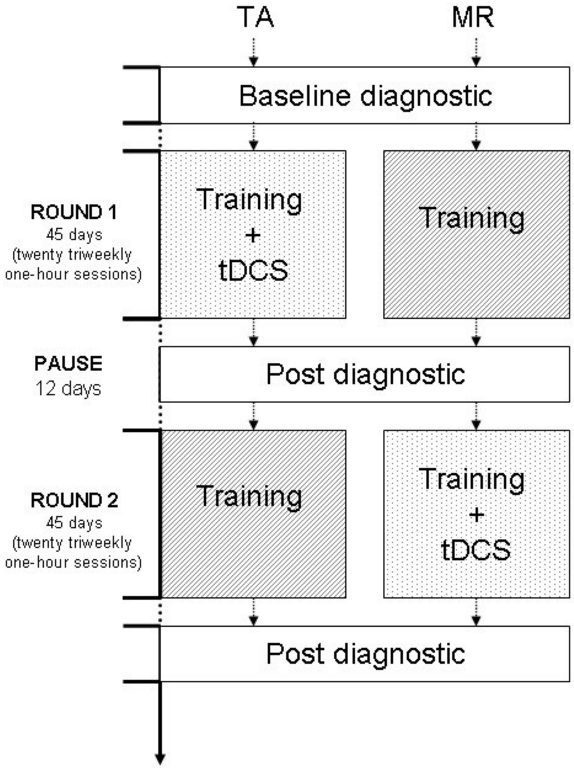


Figure 1 - Study design. Both patients underwent a baseline diagnostic test when the study start. TA underwent twenty triweekly sessions of one-hour blindsight training. The firsts 30 min of the training were combined to tDCS. After two weeks pause, he underwent twenty triweekly sessions of training alone. MR underwent the same rehabilitation in the reverse order. At the end of each training round, patients underwent a post training assessment

TA was a 39-year-old right-handed salesman (Table 1). He presented with right HH due to a first-ever unilateral embolic infarction in the left hemisphere. His ischemic lesion was located on the left paramedial occipital cortex. Patient TA had a corrected-to-normal visual acuity and was able to maintain fixation. He was alert and cooperative. The rehabilitation program started 12 months after the event causing the visual field defect.

MR was a 27-year-old right-handed unemployed woman who presented with left HH (Table 1). Magnetic resonance imaging showed a right parieto-occipital first-ever ischemic stroke. She had normal visual acuity and was vigilant and compliant and able to maintain fixation. Her rehabilitation program started 14 months after the event causing the visual field defect.

Table 1: Characteristics of patients

Case	Gender	Age	Side of Lesion	Type of Lesion	Age of the Lesion
TA	Male	39	Left	Ischemic	12 months
MR	Female	27	Right	Ischemic	14 months

Patients underwent blindsight therapy in two rounds of training.

TA underwent tDCS during the first round of rehabilitation, MR was treated with tDCS during the second round of rehabilitation. Each round is composed by twenty one-hour sessions of training occurring three times a week with a two-week interval between two rounds (see Fig.1).

During each one-hour session, the patients were seated in front of a 19-inch monitor with a white screen in background at a distance of 50 cm, sub-tending a visual angle of 45° × 27°, in a darkened room. Patients were asked to maintain central fixation and were exposed to visual stimuli in their blind hemifield. The patients' task was to detect and/or discriminate between stimuli. They were presented according to a random sequence with respect to exposure time (from 1 to 10 s), color, shape (geometrical figures or letters), and frequency (from 0 to 5 Hz). The size of each stimulus was subtended approximately by 5°–2° of visual angle (dimension of the stimuli varied from 5 to 2 cm). The patients were subjected to around

700 different stimuli variously associated in space and/or time. During all the exercise times, fixation stability was required of the patient, and this was monitored by a Tobii X2 eyetracker.

tDCS treatment was carried out simultaneously to the training in one round. The stimulation started at the beginning of the rehabilitation session, and continued for the firsts 30-min training period, then tDCS stopped and training continue in order to complete the one-hour session.

Anodal tDCS was applied, using a battery-driven constant current stimulator (BrainStim, E.M.S. s.r.l., Bologna, Italy, http://brainstim.it), and a pair of surface saline-soaked sponge electrodes (5 × 5 cm). Current intensity was 2 mA (Fade-in/-out = 10 s), for a total duration of 30 min. The anode was placed over the parieto-occipital cortex of the affected hemisphere (PO4 for TA. PO3 for MR; according to the international reference EEG 10-20 system). The cathode was placed in the contralateral supraorbital position.

To assess the improvement after rehabilitation, we used clinical, functional, and ecological endpoints.

Clinical-instrumental assessment: A threshold visual field Humphrey SITA-standard 30-2 program was used to measure the central 30 degrees of visual perception. To treat perimetric data, the Sahraie et al. method 21) was used.

For peripheral visual field testing, the Schuhfried Vienna PP-R test was used to measure visual perception up to 180 degrees. During the test, a second simultaneous task in central vision (following a moving target) was performed in order to verify test reliability.

Functional visual field assessment: The test for attention performance (TAP, v. 2.3) visual field 92 stimuli subtest (Leclerq et al., 2013) was performed.

Ecological assessment: During the initial and final interviews, data for an International Classification of Functioning (ICF) profile of the subject was collected. The profile included mainly the activity and participation categories of ICF as recommended by de Haan et al. (2014). A clinical assessment was also carried out to verify the absence of confounding factors such as comorbidities, including neurological, psychiatric, or ophthalmological pathology and to exclude the presence of visuo-spatial neglect. In order to verify satisfaction of the inclusion criteria for non-invasive brain stimulation (Bikson et al., 2016), clinical and instrumental investigations were performed before treatment.

3.3 Results

None of the patients reported any complications or adverse events associated with rehabilitation treatment and tDCS.

TA Quality of fixation, registered by means of the TobiiX2 eyetracker, was registered as stable. During rehabilitation, his fixation remained stable and the standard deviation of the fixations was 1.35 degrees.

As shown in Table 2, the TA sensitivity in the blind hemifield in the threshold test increased by 35.5 dB (+103%) after training combined with tDCS, and it improved by only 3 dB (+4%) after training without tDCS.

The TA Schuhfried Vienna PP-R test showed an increase in the peripheral stimuli perception by 35 degrees (from 95° to 130° - that represents an improvement of 37%) with an enhanced accuracy in tracking task (deviation from 14 to 4.2 mm). At the end of second training round—without tDCS—we observed a further enlargement of peripheral perception of 13° (+10%) and the accuracy was almost stable (from 4.2 to 5.3 mm).

The TA TAP Battery subtest of the visual fields recorded 4 points (of 46 points tested in the affected hemifield) at the patient's baseline. After training with tDCS, the detected stimuli increase to 10, and after training without, they were 11. Therefore, we observed a gain of 6 points (+150%) of vision after the first round, and one additional point after the second round (+10%).

Regarding the response speed, for TA there was a decrease of reaction time after both rehabilitative rounds, averaging 212 ms after the rehabilitation combined with tDCS and 98 ms after blindsight rehabilitation alone.

As regards the ecological improvement, the rehabilitation had a positive effect in all ICF codes considered (Table 3).

In particular, as observed from the subjective qualitative questionnaire, TA reported an improvement in the perception of people and objects in his blind hemifield. Although he was not able to define them clearly, he felt their presence. The patient also often noticed a distorted view at the edge of the scotoma, with elongated shapes and washed out colors.

MR quality of fixation, registered by means of the TobiiX2 eyetracker, was registered as stable. During rehabilitation, her fixation remained stable, as indicated by the standard deviation of all fixations in every session of 0.9 degrees. As shown in Table 2, after the first training round—without tDCS— MR sensitivity in the affected hemifield documented an increase of 69.5 dB (+41%). After the second round, the testing showed a further improvement of 201.5 dB (+85%) associated with tDCS. Both the stimulus detection and tracking tasks were stable in the Schuhfried Vienna PP-R test after the first round of rehabilitation. After the second round of rehabilitation with tDCS, peripheral stimulus detection increased by 45 degrees (35%) and the tracking task improved by 0.4 mm.

At baseline, patient MR recorded 20 out of 46 stimuli in her blind hemifield in the TAP test. After the first rehabilitation round, the detected points remained unchanged, and after the tDCS rehabilitation round, they increase to 29 (+45%). Patient MR show an average reduction of response time of 7 ms after blindsight rehabilitation and a further reduction of 416 ms more after rehabilitation combined with tDCS.

The rehabilitation had a positive effect in all ICF codes considered (Table 4). In particular, MR regained an independent life. She was able to return to living independently (she went to live in her parent’s house after the event) and was able to take care of her son and resume gainful employment.

Table 2: Clinical-instrumental and functional assessment for TA and MR. Outcome variables in absolute values and in percentage of change are reported. VF sensitivity: value in decibel in Humprey SITA-standard 30-2 program; VF extension: total extension in degrees of vision in Vienna Schuhfried PP-R test; Detected stimuli: number of perceived stimuli in affected hemifield in TAP, v. 2.3, visual field 92 stimuli subtest; Reaction time: average of reaction time in the affected hemifield in TAP, v. 2.3, visual field 92 stimuli subtest.

Case	Assessment	Baseline	After Round 1		After Round 2	
		Abs. value	Abs. value	% of change	Abs. value	% of change
TA	VF sensitivity (dB)	34.5	70	103%	73	4%
	VF extension (deg.)	95	130	37%	143	10%
	Detected stimuli (no.)	4	10	150%	11	10%
	Reaction Time (ms)	2835	2623	7%	2525	4%
MR	VF sensitivity (dB)	168.5	238	41%	439.5	85%
	VF extension (deg.)	134	130	3%	175	35%
	Detected stimuli (no.)	20	20	0%	29	45%
	Reaction Time (ms)	2031	2024	0%	1608	21%

Table 3: Patient TA ICF Activity and Participation Report. List of Capacity before and after training. S =Self Report, T= Test Report. Functions: d110 Watching, d155 Acquiring skills, d210 Undertaking a single task, d230 Carrying out daily routine, d360 Using communication devices and techniques, d460 Moving around in different locations, d475 Driving, d620 Acquisition of goods and services, d630 Preparing meals, d640 Doing housework, d660 Assisting others, d850 Self-employment, d920 Recreation and leisure.

Code	**Pre**	**0**	**1**	**2**	**3**	**4**	**Post**	**0**	**1**	**2**	**3**	**4**
d110	**S**	▨	▨	▨	▨		**S**	▨	▨	▨		
	T	▨	▨	▨	▨		**T**	▨	▨	▨		
d155	**S**	▨	▨	▨			**S**	▨	▨			
	T	▨	▨	▨			**T**	▨				
d210	**S**	▨	▨	▨			**S**	▨	▨			
	T	▨	▨				**T**	▨				
d230	**S**	▨	▨	▨	▨		**S**	▨	▨			
	T	▨	▨	▨	▨		**T**	▨				
d360	**S**	▨	▨	▨			**S**	▨				
	T	▨	▨				**T**	▨				
d460	**S**	▨	▨	▨			**S**	▨	▨			
	T	▨	▨				**T**	▨				
d475	**S**	▨	▨	▨	▨	▨	**S**	▨	▨	▨		
	T	▨	▨	▨	▨	▨	**T**	▨				
d620	**S**	▨	▨	▨	▨		**S**	▨	▨			
	T	▨	▨	▨			**T**	▨				
d630	**S**	▨	▨	▨	▨		**S**	▨	▨			
	T	▨	▨				**T**	▨				
d640	**S**	▨	▨	▨	▨		**S**	▨	▨			
	T	▨	▨				**T**	▨				
d660	**S**	▨	▨	▨	▨		**S**	▨				
	T	▨	▨	▨			**T**	▨				
d850	**S**	▨	▨	▨			**S**	▨				
	T	▨	▨	▨			**T**	▨				
d920	**S**	▨	▨	▨			**S**	▨				
	T	▨	▨	▨			**T**	▨				

Table 4: Patient MR ICF Activity and Participation Report. List of Capacity before and after training. S =Self Report, T= Test Report. Functions: d110 Watching, d155 Acquiring skills, d210 Undertaking a single task, d230 Carrying out daily routine, d360 Using communication devices and techniques, d460 Moving around in different locations, d475 Driving, d620 Acquisition of goods and services, d630 Preparing meals, d640 Doing housework, d660 Assisting others, d850 Self-employment, d920 Recreation and leisure.

Code	Pre	0	1	2	3	4	Post	0	1	2	3	4
d110	S	▨	▨	▨	▨		S	▨	▨			
	T	▨	▨	▨	▨		T	▨	▨			
d155	S	▨	▨	▨	▨		S	▨	▨	▨		
	T	▨	▨	▨	▨		T	▨				
d210	S	▨	▨	▨			S	▨	▨			
	T	▨	▨	▨			T	▨	▨			
d230	S	▨	▨	▨	▨	▨	S	▨	▨	▨		
	T	▨	▨	▨	▨		T	▨	▨			
d360	S	▨	▨	▨	▨		S	▨	▨			
	T	▨	▨	▨	▨		T	▨				
d460	S	▨	▨	▨	▨		S	▨	▨			
	T	▨	▨	▨			T	▨				
d475	S	▨	▨	▨	▨	▨	S	▨	▨			
	T	▨	▨	▨	▨	▨	T	▨	▨			
d620	S	▨	▨	▨	▨		S	▨	▨			
	T	▨	▨	▨	▨		T	▨	▨			
d630	S	▨	▨	▨	▨	▨	S	▨				
	T	▨	▨	▨	▨		T	▨				
d640	S	▨	▨	▨	▨	▨	S	▨	▨			
	T	▨	▨	▨	▨		T	▨				
d660	S	▨	▨	▨	▨	▨	S	▨	▨			
	T	▨	▨	▨	▨		T	▨				
d850	S	▨	▨	▨	▨	▨	S	▨	▨	▨		
	T	▨	▨	▨	▨		T	▨				
d920	S	▨	▨	▨	▨	▨	S	▨	▨			
	T	▨	▨	▨	▨		T	▨				

3.4 Discussion

Both patients showed major positive training effects when blindsight exercises were combined with tDCS.

From the clinical-instrumental point of view in the threshold test, we observed an improvement of visual field sensitivity with a higher improvement when tDCS is utilized for rehabilitation. This led us to think that tDCS could enhance the effects of rehabilitation. From the functional point of view, a two-fold positive effect was induced by the TAP battery.

Improvements occurred in visual perception and response speed in stimulus detection. Interestingly, reaction times became faster after tDCS-rehabilitation (Poggel et al., 2015).

Furthermore, to the best our knowledge, this is the first study of HH rehabilitation with a computerized evaluation of up to 180 degrees to test the effectiveness of the treatment on the extremes of peripheral vision (using the Schuhfried Vienna PP-R). The degree of peripheral visual field extension in the PP-R test increased after rehabilitation treatment. This is probably the reason for the improvement in the patients' quality of life. Given that space exploration and mobility are the most impaired functions in hemianopic patients (Gall et al., 2009), improved lateral visual field usage allowed the resumption of key activities of daily living such as driving, cooking, and leisure time pursuits.

When we analyzed the ICF profile (Tables 3 and 4), it was noted that the capacity increased after rehabilitation. This supports the idea that there had been improvement in the patient's ADLs and social life activity (Gall et al., 2008). The monitoring and the checking of stability fixation by means of eyetracker during rehabilitation sessions led us to exclude the possibility that the observed improvements can be induced by compensative eye movements (Reinhard et al., 2005).

Therefore, the two cases presented here show for the first time that ipsilesional parieto-occipital anodal tDCS influences the effects induced by blindsight treatment. It can be argued that stimulation of visual associative areas is useful to promote and enhance the blindsight phenomenon.

Our previous paper (Matteo et al., 2016) strongly suggest that blindsight rehabilitation improves the processing of visual stimuli, so it is possible that stimulation of associative areas could facilitate this processing mechanism.

We have reason to believe that even in these patients, this may have occurred by way of the cortical rearrangement via long-term potentiation mechanisms (Cooke et al., 2006). The neuroplasticity hypothesis is consistent with the literature concerning border rehabilitation associated with tDCS, (Plow et al., 2001; Plow et al., 2012; Plow et al., Alber et al., 2017; Halko et al., 2011). In light of this primary results, we recommend further studies to investigate the tDCS effects on blindsight treatment in HH.

Although there is presently no evidence in the literature regarding the best stimulation protocols and electrode montage to obtain the greatest rehabilitation effect on HH (Mahmoudi et al., 2011), the hypothesis of anodal stimulation over PO3 and PO4 merits further investigation.

In conclusion, the results of the two case studies indicate that positive effects could occur after rehabilitation treatment of HH, by enhancing blindsight. This is consistent with prior reports in the literature (Sahraie et al., 2010; Sahraie et al., 2013). The results obtained in these two case reports seem to be promising. However, it is not possible to generalize from these individual cases: the results show an improvement but they do not provide conclusive or statistical evidence. Thus, our two case study may be able to guide further studies in order to validate the results with a larger population, using a sham-controlled study design, with correlated functional images and monitoring of the long-term stability using an appropriate series of follow-up evaluations.

4. Project III: Non-invasive electric current stimulation in the treatment of homonymous hemianopia

4.1 Introduction

Homonymous hemianopia is considered a permanent visual loss of one hemifield. Recent studies applying vision restoration methods such as visual training and non-invasive electrical stimulation are shown to be effective for the treatment of optic nerve damage suggesting plasticity processes within the visual system. However, the potential clinical application of alternating current stimulation in homonymous hemianopia after stroke is still unexplored. The aim of the study is to explore if alternating current stimulation alone or combined with direct current stimulation induce significant increase in the visual field as compared to sham stimulation in hemianopic patients.

4.2 Methods

Study design

24 participants were randomized into three groups of eight.

Each group received a different treatment: 1) Sham tDCS and sham ACS; 2) Verum tDCS and Verum ACS; 3) Sham tDCS and Verum ACS.

A total of three assessments were carried out: the baseline at least 48 hours prior intervention, the second one immediately after intervention, and the follow-up eight weeks after the end of the treatment.

Subjects

The patients included in the study were patients above 18 years who presented: HH due to ischemic or haemorrhagic stroke, with a cronic lesion age (at least 6 months) and visual acuity at least 0.4.

Patients presented eye or central nervous system diseases or any exclusion criteria for the non-invesive brain stimulation therapy (Antal et al., 2017) were excluded from the study.

Intervention

Each group received 10 daily stimulation sessions (30 min) within a period of 2 weeks
In the Alternating Current Stimulation the stimulating electrode were placed at Fpz (10–20 EEG system) and the reference electrode on the right arm. The intensity was below 1.5 milliampere and the duration was 20 minutes. In the ACS-sham condition patients received occasional current bursts causing a weak sensation of phosphenes.
In the Direct Current Stimulation (applied for 10 minutes before ACS) the stimulating electrode were placed over the occipital cortex and the reference electrode at Fpz. The intensity was set at 1 milliampere.
In the tDCS sham condition, patients received only the fade in/fade out for 30 seconds causing the skin sensation similar to the real stimulation.

Endpoints

The primary endpoints were the percentage of change after treatment in Detection Accuracy assessed by HRP and the Mean Sensitivity assessed by standard static perimetry. Secondary endpoints included foveal sensitivity, fixation, visual acuity and contrast vision.

The change after treatment was calculated in percentage respect to the baseline.

4.3 Results

Due to the small sample size, non-parametric statistical analysis was used.

No significant difference was found between groups at baseline level.

Kruskall Wallis one-tail test revealed a significant difference between the three groups after treatment in Standard Perimetry outcome.

Groups differs in Foveal sensivity in ipsilesional eye (p=0.006) and Mean Sensitivity in ipsilesional eye (p=0.025) and contralesional eye (p=0.022).

Post-hoc Mann Whitney tests revealed after treatment Alternating Current group showed a significant decrease in bilateral Mean Sensitivity and both Active groups showed a significant increase in Foveal Sensitivity in the ipsilesional eye.

At follow-up these differences were no more evident; however the fixation rate differs across groups in ipsi (p=0.031) and contralesional eye (p=0.027). Active groups showed better bilateral Fixation in comparison to sham group.

4.4 Discussion

Main Conclusions

1. The study did not show a significant increase in the visual field by means of rtACS and tDCS/rtACS in homonymous hemianopia. Given the increase in foveal sensitivity observed in AC stimulation group, it may be that with the present stimulation parameters it leads to improvements in central vision rather than peripheral.

2. The worsening in Mean Sensitivity after rtACS but not after combined tDCS/rtACS suggests different mechanisms of action between both methods. It could be that rtACS is more feasible for the treatment of optic nerve damage or to improve central vision.

3. The baseline differences in visual function between ipsi and contralesional eyes must be taken into account to define more accurate and individualized treatments.

4. Further studies are needed to explore if the combination of tDCS/rtACS could have clinical applications.

Kind of current

The group treated with the AC (Alternating Current) stimulation had a significant worse of the visual field respect to the sham group.

The group treated combining the AC (Alternating Current) and DC (Direct Current) did not present a worse visual field respect to sham group.

Visual field sensitivity worsened, with respect to sham, only in the group of alternating current stimulation alone, the visual field did not degraded in the group where the alternating current stimulation was combined with the direct current stimulation: when tDCS was used in combination with tACS we did not observe a worsening in the visual field.

It appears that tDCS has a "protective" factor on the worsening induced by the tACS: it seems that tDCS stops the worsening effects of alternating current on the visual field.

Obviously, due to the small number of the tested people, it is not possible to generalize any concept because it is possible that other factors could have influenced the observed results, particularly when we speak about the combination between direct and alternating current stimulation.

The effects of direct and alternating current stimulation of the brain are, worldwide, largely studied but, as resulted from our tests, the two kinds of stimulation had different mechanisms on the hemianopic brain.

Electrodes position

For the stimulation by means of the alternating current, the elctrodes were placed in a periorbital position; this because it was demonstrated a resynchronization and modifications of cortical networks following the tACS applied in the forehead (Bola et al., 2014). The tACS was applied to the patient by means a forehead electrode and the reference electrode on the right arm.

For tDCS, two stimulations were performed at the same time:

- the anodal stimulation of the affected hemisphere: anode was positioned in the ipsilesional occipital area with the reference electrode on the ipsilesional forehead

- the cathodal stimulation of the intect hemisphere: cathode was placed in the contralesional occipital area with the reference electrode on the contralesional forehead

That configuration was designed to re-balance the two hemispheres. In fact, it was registered a hyperactivity in the contralesional hemisphere related to a reduced activity in the damaged hemisphere following the stroke (Kinsbourne, 1977).

The position of electrodes could be a factor that influences the effectiveness of the treatment.

For example, when the brain stimulation is performed using ACS, it is possible that a different electrodes montage (closer to the damage) would be more effective in the hemianopia's care.

A stimulation physically closer to the damaged area could be more effective; in this way, the electrical current should arrive directly, without dissipations, to the damaged area.

Future studies addressing the better electrodes position could be useful to prove if Alternating Current Stimulation could have positive effects on visual field in hemianopia.

Foveal vision improvement

After treatment, both the active groups (stimulated with alternating current alone and with alternating current alternate with direct current) showed a better ipsilesional foveal vision: we observed an improvement in foveal sensitivity of the ipsilesional eye.

This result is consistent with the previous literature papers that state an improvement of central vision following alternating current stimulation (Sabel et al., 2004; Anastasiou et al., 2013; Shinoda et al., 2008).

It is not possible to say if the tDCS is effective too, but it is possible to state that a deeper investigation, to better understand the specific effects in stimulation by using the alternating current for retinal diseases or central vision impairment (i.e. Age-related macular degeneration), is recommended.

The central area is part of the visual field (also if it is tested separated by the device) and it is a fundamental component of vision. The central vision is so important that, in ophthalmology, it is considered as a standard of visual function assessment: it is related to the visual acuity. In fact, the vast majority of optic nerve fibres convey information regarding central vision (Rogers, 2010).

When the alternating current pass through the optical nerve, it happens the stimulation of the nervous tissue more ascribed to the central vision. The potentiation of central vision could be related to a weakness in the peripheral area lacking energy that is concentrated into the central vision.

Follow-up

At follow-up, two months after the treatment, the effect of the treatments on visual field and foveal threshold disappeared, but both the active groups showed a better fixation.

The differences in visual field sensitivity are not more evident at follow-up; the improvement occurred after the treatment does not last over time. During the two months between the end of the treatment and the follow-up evaluation, something happened: both active groups showed a better fixation. It could be possible that the central vision (foveal threshold) should have changed the fixation ability.

The fixation and central vision are strictly related (Abdelnour et al., 2001). In fact, the more the foveal provide detail for central vision, the greater fixation has the elements to stay stable.

In fact, when pathologies alter the foveolar fixation (i.e. Age-related macular degeneration, strabismus amblyopia etc.) the more fixation is far from foveal (very central retina) the greater vision decrease.

In the case of alternating current stimulation an improvement in foveal vision should be related to a more stable eye, a crucial factor when evaluating patients with hemianopia.

Perspectives

The analysis of the results obtained through our experimentation leads us to the conclusion that it was not exhaustive: there are still too few certainly answers and too many are the outstanding questions.

The original project design (Gall et al., 2015) belonged three centers:

- a two-arms in Italy aimed to discover the effects of tDCS compared to sham stimulation;
- a two-arm in Finland aimed to discover the effects of alternating current stimulation compared to sham stimulation;
- a three-arm in Germany aimed to discover the effects of alternating current stimulation alone, alternating current stimulation associated to direct current stimulation, and sham stimulation.

In the next future it will be interesting to compare and analyze together all the results of the three centers included in the REVIS study (Rome and Finland, too). Crosschecking and analyzing all the data it will be possible to eliminate some confounding's factors and to verify the rightness of some of the hypothesis here stated.

5. General Discussion

Literature summary

Even though the first approach to direct current stimulation are back to 60s (Bindman 1964), the firsts approach on visual system appears from 70s (Dobelle und Mladejovsky 1974) when the current stimulation effect on the visual system was studied producing the phosphenes.

Afterward, to answer the question of what the stimulation parameters were to determine the phosphenes vision, a large number of studies have been performed. (Turi et al., 2013; Schutter et al., 2010; Kar et al., 2012; Kanai et al., 2008; Naycheva et al., 2012; Fujikado et al., 2006; Raco et al., 2014; Terhune et al., 2015; Antal et al., 2003a; Antal et al., 2003b; Chaieb et al., 2007; Delbeke et al., 2003; Kanai et al., 2010).

In these clinical investigations were examined patients with different causes of visual impairments and healthy subjects, respectively 118 and 196, were examined. Based on that, it is now a fact that the phosphenes occurrence depends on stimulation frequency and current strength.

It has also been shown that the stimulation with current modulates the brain activity: this was observed and recorded by VEP, EEG, and electro-retinography. Generally, an enhancement of the alpha activity and/or a stronger connectivity of the different parts of the visual cortex was registered. (Antal et al., 2004a; Antal et al., 2004b; Chaieb et al., 2007; Costa et al., 2015; Reinhart et al., 2017; Sczesny-Kaiser et al., 2016; Strigaro et al., 2015; Ding et al., 2016; Halko et al., 2011; Spiegel et al., 2013; Bola et al., 2014; Schmidt et al., 2013; Kurimoto et al., 2011; Naycheva et al., 2013). In total, 75 patients with different visual impairments and 185 healthy subjects participated to these investigations.

Specific visual tasks, in subjects treated with the electrical brain stimulation, may worsen or improve. Many studies, involving 251 healthy subjects, were performed to demonstrate the correlation between electrical stimulation and its effects on visual tasks. (Kar et al., 2014; Laczó et al., 2012; Kanai et al., 2010; Brignani et al., 2013; Xie et al., 2011; Cosman et al., 2015a; Costa et al., 2012; Costa et al., 2015b; Kraft et al., 2010; Reinhart et al., 2016; Richard et al., 2015).

It is important to highlight that there are significant differences when treating healthy subjects or visually impaired persons with electrical current stimulation.

The first approach to treat visual impairment by means of the stimulation with current is from Shinoda et al., 2008. This first, preliminary, study conducted on Age-related Macular Degeneration (AMD) recognized an improvement of best-corrected visual acuity after transcorneal alternating current stimulation.

Afterward, many studies conducted for assessing if the electrical current stimulation was useful in restoring the visual function in visually impaired patients, were published. It was shown that the current stimulation is effective in restoring function in three different districts of the visual pathway systems: in the retinal district, in the optic nerve district and in the visual brain district.

In particular, we found evidence in the treatment of glaucoma, age-related macular degeneration, optic nerve damage, optic neuropathy, retinal dystrophy, diabetic retinopathy, retinitis pigmentosa, retinal artery occlusion, amblyopia and also myopia. The following table reports the list of papers and the treated condition.

Visual pathway district	Kind of stimulation	Conditions	First author and year
Retina	ACS, RNS	· Age-related macular degeneration · Macular dystrophy · Retinal artery occulsion · Retinitis Pigmentosa · Myopia	Anastassiou 2013, Shinoda 2008, Ozeki 2013, Naycheva 2012 , Schatz 2011, Morimoto2006, Inomata 2007, Camilleri 2014, Camilleri 2016, Fujikado 2007,
Optic nerve	ACS	· Glaucoma · Optic nerve damage · Optic neuropathy	Sabel, 2011; Gall 2016, Gall 2011, Bola 2014, Fujikado 2006 , Fedorov 2011, Naycheva 2013, Oono 2011, Schatz 2017
Brain	ACS, RNS, tDCS	· Hemianopsia · Brain trauma · Ambliopia	Gall 2013, Schmidt 2013, Gall 2010, Campana 2014, Alber 2017, Cowey 2013, Ding 2016, Halko 2011, Olma 2013, Plow2011, Plow 2012, Plow 2012, Spiegel 2013, Spiegel 2013

As above reported, many visual pathologies with a so various scenario on the pathogenesis could be treated by means of the electrical stimulation, but the main question was: why?

A paper by Sabel et al., published in 2011, answers to the question: the authors proposed the “residual vision activation theory”.

The theory is based on the fact that the loss of vision in stroke, neurotrauma, glaucoma, amblyopia and age-related macular degeneration, usually, is not complete: some structures are typically spared by the damage. Engaging the residual structure in repetitive electrical stimulation the neural tissue can be reactivated and restored.

The stimulation can be done by means of a repetitive and non-invasive electrical brain current stimulation. The stimulation can have the effect to strength the synaptic transmission, to synchronize the partially damaged structures (within-systems plasticity) and, downstream, to reconnect the neuronal networks (network plasticity).

Stimulation methods

The pathologies were treated with transcranial direct current stimulation (tDCS) or alternating current stimulation (tACS) and, in addition, with the random noise stimulation (tRNS, a random amplitude and frequencies alternating stimulation).

In tDCS, the stimulation current intensity is constant on time. This is the most used and studied kind of current stimulation in rehabilitation. tDCS can be anodal or cathodal. Normally, anodal has excitatory effects on brain, while cathodal has inhibitory effects.

tACS is a stimulation where the current intensity is time dependent with a sinusoidal shape. The description of this stimulation could be done by means of amplitude, frequency and phases data. tACS is supposed to facilitate the re-syncronization of the brain in neuro rehabilitation.

tRNS is a type of ACS where the stimulation values varied randomly. tRNS is the mostly recent used in neuro rehabilitation and its effects on the brain are promising but the mechanisms of action on brain are not yet completely clear.

Stimulation parameters

About the electrical stimulation, two main factors have to be considered: the usage of electrodes and the current delivery.

One of the main difference between the stimulation methods is represented by the place where the electrodes to deliver the electrical current for stimulation are placed.

In any event, the design of the electrodes location is such that the current's flow passes through the eyes and the brain structures involved in the visual process.

In the tDCS, usually, the active electrode is placed over Oz (the 10-20 EEG international reference system) and the reference electrode is placed over Cz.

In the RNS the active electrode is placed, like for tDCS, over Oz but the reference electrode is normally placed on the right arm.

In tACS the stimulating electrode (one or more) is generally placed close to the orbit of the eye: normally on the forehead or on the scalp. The reference electrode position may vary; it could be placed on the right arm, near the eye or on the scalp (so the current flow could better stimulate the injured visual pathway).

In case of alternating trans-corneal stimulations, the electrode is placed directly on the cornea. Two main kinds of electrodes are used for trans-corneal: “Dawson, Trick and Litzkow electrode” (a metal coated nylon thread that is installed between the medial and lateral eyelid) or “contact lens” electrode.

About the current intensity, in the guidelines of Antal et al., 2017, the authors define Safety for low-intensity “conventional” TES as <4 mA, up to 60 minutes duration per day.

To avoid burnings and permanent tissue injuries the German authorities (Bundesanstalt für Arzneimittel und Medizinprodukte) suggest to stay within a limit of 0.1 mA/cm², (current densities >0.028 mA/cm² may sometimes be painful) and the total charge should not be higher than 216 C/cm².

The standard stimulation protocol used in human trials are: ≤40 min, ≤4 milliamperes, ≤7.2 Coulombs, well under the limits that cause damages on animals (Bikson et al., 2016).

Usually, in visual restoration, the current intensity used for tDCS is about 2 mA, whereas the intensity for tACS is around 1.5mA peak-to-peak in the ACS as the RNS. The frequency range from 0 to 50 Hz for ACS and from 100 to 640 Hz for RNS.

Multiple daily stimulation sessions are usually applied and the duration is about 20-30 min per day.

Safety

One of the main aspects about the treatment of patients with the electrical current is the safety aspect: its assessment is of paramount importance.

The safety aspect, when using the electrical current for brain stimulation on all the pathologies was analyzed in different studies.

A recent review (Russo et al., 2017), analyzed 86 papers in order to find the occurrence of tDCS adverse effects in stroke patients. The authors found that only 11% of published papers report the occurrence of side effects. The most common was itching (70%), followed by burning sensation (40%), headache (40%), tingling (30%), sleepiness (20%), difficulty of concentration, mild fatigue, skin redness, and dizziness (10%).

Another review (Bikson et al., 2016) performed the analysis on Safety using Direct current stimulation. In this work, the authors measured the frequency of Serious Adverse Effects (SAE) considering the stimulation parameters like intensity, duration, density, charge, and charge density. Considering more than 33000 sessions over 1000 subjects, they concluded that the protocols usually used for the humans did not produce any SAE or irreversible injury.

Regarding safety, alternating current stimulations looks safer than direct current stimulation.

Fertolani et al. (2015) found that the application of alternating current stimulation over the scalp induced less sensation compared with transcranial direct current stimulation. Therefore, anodal tDCS induced more annoyance compared to other tES.

We hereby suppose the reason: in alternating current stimulation, the area under the curve of current intensity on time is set to be equal, under and above the null value. Due to this layout, we obtain an equal number of charge in time. This leads the ions towards and away from electrodes preventing the tissues damage and electrodes corrosion.

When using current stimulation to restore vision, the most common reported side effects are the same observed in other medical applications: itching, pitching, tingling and warmth sensation below the stimulation electrode.

The more general adverse events that occurred, even if rare, are: weak headache, drowsiness or poor sleep, occasional blood pressure fluctuations, dizziness and general fatigue.

Analyzing the studies aimed at restoring the visual system by means of tDCS, for a total of 164 patients, we did not find any SAE. (Campana et al., 2014; Alber et al., 2017; Cowey et al., 2013; Halko et al., 2011; Ko-Un et al., 2016; Olma et al., 2013; Plow et al., 2011; Plow et al., 2012a; Plow et al., 2012b; Ding et al., 2016; Spiegel et al., 2013a; Spiegel et al., 2013b).
The only adverse events found in literature related to tDCS for visual impairment are “occasional itching or tingling” (Alber et al., 2017) and “slight tingling sensation under the electrodes” (Spiegel et al., 2013b). It is to be pointed out that in all these studies only one patient withdrew because of discomfort (Spiegel et al., 2013a); and the authors stated: “there were no adverse effects during or following tDCS"

The same level of safety was found analyzing the studies aimed at restoring the vision by means of Alternating current stimulation. (Sabel et al., 2011; Gall et al., 2016; Gall et al., 2011; Fedorov et al., 2011; Schmidt et al., 2013; Gall et al., 2010; Gall et al., 2013; Bola et al., 2014; Terhune et al., 2015; Anastassiou et al., 2013; Shinoda et al., 2008).

Among 627 treated people, in rare cases (<10%) the patients treated with trans-orbital stimulation reported cutaneous sensations and in sporadic cases (<5%) patients experienced mild headache, general fatigue, dizziness or blood pressure fluctuations. These mild accompanying effects are benign and do not raise concerns about the safety of stimulation with alternating current for vision restoration.

The only adverse event considered as “serious” after stimulation with Alternating electrical current (Transpalpebral) is a dermatitis on both superior lids, occurred in a 62-year-old man (Shinoda et al. 2008). In that specific case, despite the strong preference of the man to continue the treatment, researchers decided to stop it.

Transcorneal stimulation with alternating current (TES) was performed over 194 visually impaired patients. (Ozeki et al., 2013; Naycheva et al., 2012; Schatz et al., 2011; Morimoto et al., 2006; Inomata et al., 2007; Fujikado et al., 2006; Fujikado et al., 2007; Naycheva et al., 2013; Oono et al., 2011; Schatz et al., 2017)

The following side local effects were reported: foreign body sensation, dry eye, and transient superficial keratitis. About 15% of the patients being treated with transcorneal electrical stimulation reported dry eye and <3% reported foreign body sensations in the eye. In rare case (<6%) patients suffered a transient superficial or punctate keratitis (non-detectable to the sit-lamp examination and healed by the next day).

This kind of side effects could be related to the electrode kind. In fact, the transcorneal electrical stimulation is applied with some electrodes directly in touch with the cornea that is one of the most sensitive parts of the human body.

The study of Random Noise Stimulation on visually impaired patients been tested over 45 patients. (Camilleri et al., 2014; Camilleri et al., 2016; Campana et al., 2014). None of them reported any side effects during or after treatment.

Finally, there was no report of any single serious adverse event (SAE) in all these studies using tDCS, tACS, TES and RNS on visual system.

Considering the low frequency and the low level of concern of the adverse events reported with >1000 visually impaired patients that have undergone the stimulation with current in different institutions and different treatment protocols, it is possible to state that the use of the electrical stimulation, for the treatment of vision loss, can be considered safe.

Efficacy of current stimulation in restoring vision

The results obtained from most of the studies are promising: they demonstrate the efficacy of current stimulation in restoring vision when the vision loss is caused by a variety of ophthalmological or neurological disorders. Statistical and clinically relevant effects were achieved.

The patients, suffering from various visual impairments, treated with electrical stimulation registered one or more of the following advantages:

1. Improved visual acuity VA (or BCVA)
2. Improved contrast sensitivity
3. Improve stereopsis
4. Enlarged visual field
5. Augmented detection accuracy in the visual field
6. Change in brain activity measured by EEG or VEP
7. Subjective improvements reported by the patient (with respect to color vision, contrast sensitivity, blurred vision, acuity, visual field expansion or others).

The Alternating current stimulation was demonstrated to be effective in improving visual field, improve visual acuity, contrast and change alfa-band brain activity.

With the large sample of patients reported by Fedorov et al. (2011), it has been shown that visual acuity (VA) significantly increased in both eyes (right = 0.02, left = 0.015; $p < 0.001$) and visual field (VF) size increased in the right and left eye by 7.1% and 9.3% ($p < 0.001$), respectively. VF enlargements were present in 40.4% of right and 49.5% of left eyes.

The best methodological study (multicenter, prospective, randomized, double-blind, sham-controlled trial) with the biggest sample size was carried out by Gall et al. (2016). People with different pathologies (91 subjects with Glaucoma, AION, and other optic atrophy) participated to this study. Results show that the ACS led a mean improvement of visual field of 24.0% significantly greater than after sham-stimulation (2.5%). This improvement persisted for at least 2-months.

Direct Current Stimulation demonstrated effective in improving contrast, stereopsis, motion perception, visual field and VEP.

The larger sample of patients is reported by Ding et al., 2016. The authors tested 21 amblyopic patients (both eyes) and 27 normal-vision subjects (one eye randomly selected).

They underwent separate sessions of anodal, cathodal or sham tDCS over visual cortex. Contrast sensitivity and pattern VEP were tested.

As a result, it was found a specific effect of anodal tDCS in increase VEP amplitude and contrast sensitivity for amblyopic eyes. Similar effects were found for control eyes, however the fellow eyes of amblyopic patients did not show increased contrast sensitivity following anodal tDCS. A decrease in VEP amplitude and contrast sensitivity occurs following cathodal stimulation. They concluded hypothesizing that anodal tDCS alone might have clinical relevance for the treatment of amblyopia in adulthood.

The most relevant studies associating tDCS to training (Vision Restoration Therapy) are by Plow et al., 2012 and Alber et al., 2017; both of them were conducted on hemianopic patients.

Their study design was aimed to compare two groups of patients: one group treated with training alone, the other group was treated with training associated to tDCS. For the Plow study were recruited 6 patients per group; in Alber 7 patients for each group.

Plow et al, 2012, showed an accelerated recovery in the visual field and a greater shift of the visual field border when tDCS is associated with the training.

Alber et al., 2017 showed that the recovery in the percentage of change of the visual field stimulus detection was significantly greater when tDCS was associated with the training. Both results showed a facilitation role of tDCS in the treatment of hemianopia when it is associated with training.

The effectiveness of training associated with current stimulation was found also in Miopia when the Random Noise Stimulation is applied. The random noise stimulation was demonstrated to be effective in improving visual acuity and contrast sensitivity.

In 2014, Camilleri et al. studied the effect of RNS on myopia. They showed that the training (contrast detection task) associated with RNS improve the contrast sensitivity and the visual acuity when compared to training alone. In 2016 the same research group (Camilleri et al., 2016) divided 30 myopic patients into three groups: the first underwent training with RNS, the second underwent training with sham-RNS and the third underwent RNS alone.

The training was shown to improve Visual Acuity and Contrast sensitivity when coupled with RNS and marginal effects on Contrast Sensitivity are found with the sole administration of RNS.

Concluding remarks

Until now, many studies treating the cortical modulation by means of electrical stimulation in all neurological field and, analogously, in the visual system, have been published: the technique looks promising.

The electrical stimulation for recovery of vision is a technique that needs to be deeply investigated in all its possible applications. At the state of the art, there are still too heterogeneous stimulations parameters and end points in order to design the best protocol for each pathology.

In the ophthalmological field, it seems that the stimulation with alternating current gives good chances of recovery in patients suffering from untreatable pathologies (Glaucoma, Age-Related Macular Degeneration, Retinitis pigmentosa, etc.).

In the field of hemianopsia, there are evidence of beneficial effects in using the direct current stimulation, but not yet using the alternating current. Further studies, to assess different electrodes position, current type, and different treatment conditions, are required.

Some questions remain open and still need answers. First of all, if the electrical stimulation has to be associated with the training, or it could be effective alone.

I would like to conclude this thesis by focusing on the discussion of how difficult is to evaluate the benefit of rehabilitation in the visual system.

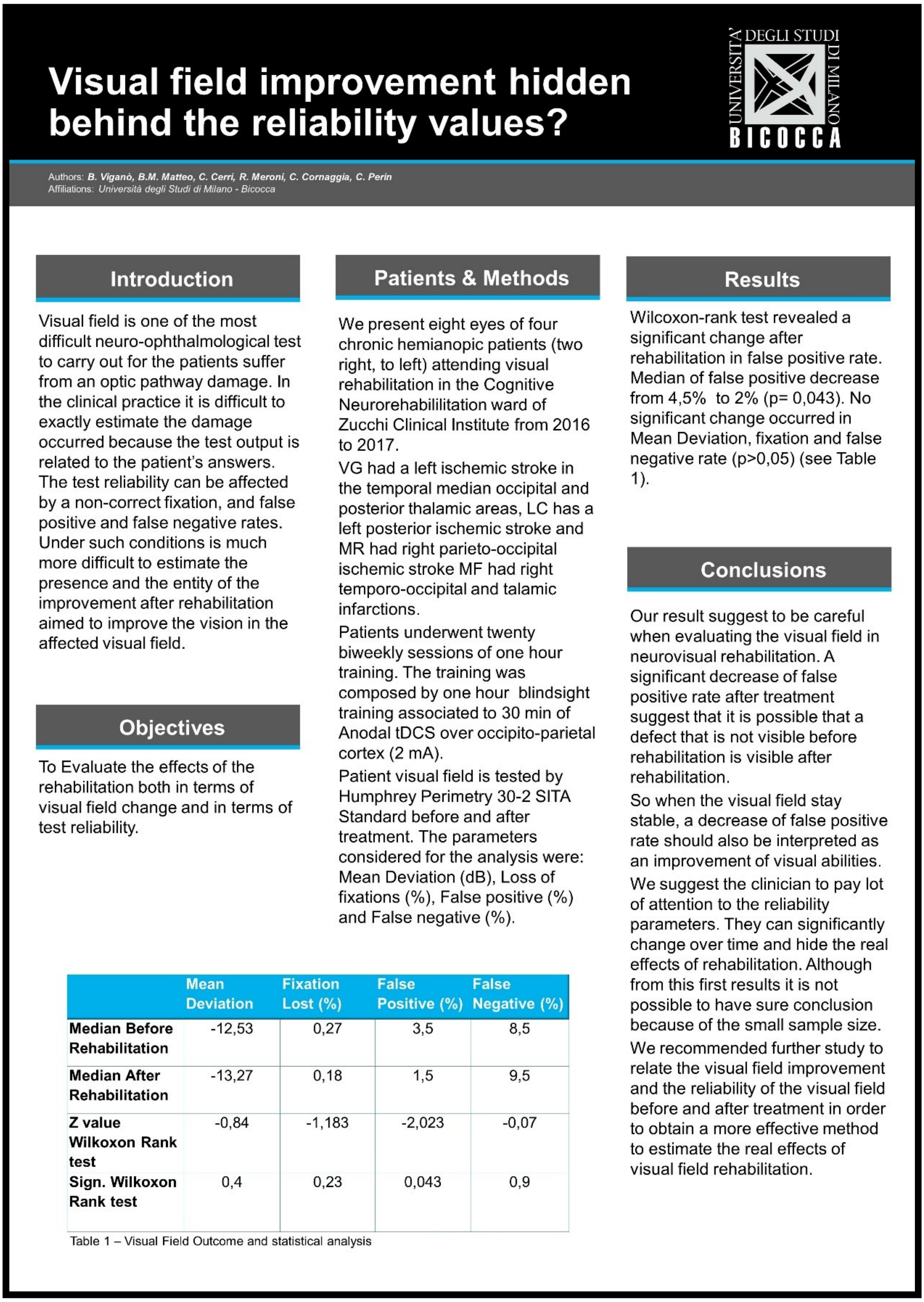
Generally, the test of visual field is very hard for the patients and the results depends on patient to patient and their conditions. Here below are reported the preliminary results of a rehabilitation study in hemianopia by means of training and tDCS (see image of poster below).

This research resulted in a Conference Paper entitled “Visual field improvement hidden behind the reliability values?” presented in the “Low Vision and Brain Conference, Berlin, 24-26 November 2017.

We did not find any improvement in visual field, but the patients had less false positive rate after treatment.

It is possible that the high false positive ratio at the beginning of the treatment masked some part of the defect. When the patients at the end of treatment are more reliable in their answers (maybe as an effect of training) the false positive rate decreases.

Our hypothesis is that the decrease of false positive rate, together with an unchanged visual field, could lead to a non-detectable improvement.



Visual field improvement hidden behind the reliability values?

Authors: ***B. Viganò, B.M. Matteo, C. Cerri, R. Meroni, C. Cornaggia, C. Perin***
Affiliations: *Università degli Studi di Milano - Bicocca*

Introduction

Visual field is one of the most difficult neuro-ophthalmological test to carry out for the patients suffer from an optic pathway damage. In the clinical practice it is difficult to exactly estimate the damage occurred because the test output is related to the patient's answers. The test reliability can be affected by a non-correct fixation, and false positive and false negative rates. Under such conditions is much more difficult to estimate the presence and the entity of the improvement after rehabilitation aimed to improve the vision in the affected visual field.

Objectives

To Evaluate the effects of the rehabilitation both in terms of visual field change and in terms of test reliability.

Patients & Methods

We present eight eyes of four chronic hemianopic patients (two right, to left) attending visual rehabilitation in the Cognitive Neurorehabililitation ward of Zucchi Clinical Institute from 2016 to 2017.

VG had a left ischemic stroke in the temporal median occipital and posterior thalamic areas, LC has a left posterior ischemic stroke and MR had right parieto-occipital ischemic stroke MF had right temporo-occipital and talamic infarctions.

Patients underwent twenty biweekly sessions of one hour training. The training was composed by one hour blindsight training associated to 30 min of Anodal tDCS over occipito-parietal cortex (2 mA).

Patient visual field is tested by Humphrey Perimetry 30-2 SITA Standard before and after treatment. The parameters considered for the analysis were: Mean Deviation (dB), Loss of fixations (%), False positive (%) and False negative (%).

	Mean Deviation	Fixation Lost (%)	False Positive (%)	False Negative (%)
Median Before Rehabilitation	-12,53	0,27	3,5	8,5
Median After Rehabilitation	-13,27	0,18	1,5	9,5
Z value Wilkoxon Rank test	-0,84	-1,183	-2,023	-0,07
Sign. Wilkoxon Rank test	0,4	0,23	0,043	0,9

Table 1 – Visual Field Outcome and statistical analysis

Results

Wilcoxon-rank test revealed a significant change after rehabilitation in false positive rate. Median of false positive decrease from 4,5% to 2% (p= 0,043). No significant change occurred in Mean Deviation, fixation and false negative rate (p>0,05) (see Table 1).

Conclusions

Our result suggest to be careful when evaluating the visual field in neurovisual rehabilitation. A significant decrease of false positive rate after treatment suggest that it is possible that a defect that is not visible before rehabilitation is visible after rehabilitation.

So when the visual field stay stable, a decrease of false positive rate should also be interpreted as an improvement of visual abilities.

We suggest the clinician to pay lot of attention to the reliability parameters. They can significantly change over time and hide the real effects of rehabilitation. Although from this first results it is not possible to have sure conclusion because of the small sample size.

We recommended further study to relate the visual field improvement and the reliability of the visual field before and after treatment in order to obtain a more effective method to estimate the real effects of visual field rehabilitation.

Then, if on one hand we can state that the current stimulation is useful, on the other hand we have a lot of work to do in order to perfecting the techniques and discover how to optimize the results.

Certainly, treating vision by means electrical stimulation, the benefit of improving visual functions outweighs by far the risks to the patient. Given that the patients that have an irreversible visually-impaired, doesn't have other options to improve their vision, this is surely a method to keep into consideration.

6. References

Abdelnour O, Kalloniatis M. (2001) Word acuity threshold as a function of contrast and retinal eccentricity. Optom Vis Sci. Dec;78(12):914-9.

Ajina, S., Kennard, C. (2012). Rehabilitation of damage to the visual brain. Revue neurologique (Paris), 168(10), 754-61.

Alber R, Moser H, Gall C, et al. (2017) Combined Transcranial Direct Current Stimulation and Vision Restoration Training in Subacute Stroke Rehabilitation: A Pilot Study. PM&R.

Anastassiou, Gerasimos; Schneegans, Anna-Lena; Selbach, Michael; Kremmer, Stephan (2013): Transpalpebral electrotherapy for dry age-related macular degeneration (AMD): an exploratory trial. In: Restorative neurology and neuroscience 31 (5), S. 571–578. DOI: 10.3233/RNN-130322.

Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, Cohen LG, Dowthwaite G, Ellrich J, Flöel A, Fregni F, George MS, Hamilton R, Haueisen J, Herrmann CS, Hummel FC, Lefaucheur JP, Liebetanz D, Loo CK, McCaig CD, Miniussi C, Miranda PC, Moliadze V, Nitsche MA, Nowak R, Padberg F, Pascual-Leone A, Poppendieck W, Priori A, Rossi S, Rossini PM, Rothwell J, Rueger MA, Ruffini G, Schellhorn K, Siebner HR, gawa Y, Wexler A, Ziemann U, Hallett M, Paulus W. (2017) Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol. 2017 Sep;128(9):1774-1809. doi: 10.1016/j.clinph.2017.06.001. Epub 2017 Jun 19.

Antal A, Kincses TZ, Nitsche MA, Bartfai O, Paulus W. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. (2004) Invest Ophthalmol Vis Sci. Feb;45(2):702-7. PubMed PMID: 14744917.

Antal A, Kincses TZ, Nitsche MA, Paulus W. Manipulation of phosphene thresholds by transcranial direct current stimulation in man. Exp Brain Res. 003Jun;150(3):375-8. Epub 2003 Apr 16.

Antal A, Kincses TZ, Nitsche MA, Paulus W. Modulation of moving phosphene thresholds by transcranial direct current stimulation of V1 in human. Neuropsychologia. 2003;41(13):1802-7. PubMed PMID: 14527543.

Antal A, Paulus W, Nitsche MA. Electrical stimulation and visual network plasticity. Restor Neurol Neurosci. 2011;29(6):365-74. doi: 10.3233/RNN-2011-0609. Review. PubMed PMID: 22124032.

Antal A, Varga ET, Kincses TZ, Nitsche MA, Paulus W. Oscillatory brain activity and transcranial direct current stimulation in humans. (2004) Neuroreport. Jun 7;15(8):1307-10.

Antal, A; Paulus, Walter; Nitsche, Michael A. (2011): Electrical stimulation and visual network plasticity. In: Restorative neurology and neuroscience 29 (6), S. 365–374. DOI: 10.3233/RNN-2011-0609.

Balliet, R., Blood, K. M., Bach-y-Rita, P. (1985). Visual field rehabilitation in the cortically blind? Journal of Neurology Neurosurgery and Psychiatry, 48(11), 1113–1124.

Behrens R, Kraft A, Irlbacher K, Gerhardt H, Olma MC, Brandt SA. Long-Lasting Enhancement of Visual Perception with Repetitive Noninvasive Transcranial Direct Current Stimulation. (2017) Front Cell Neurosci. 2017 Aug 15;11:238. doi: 10.3389/fncel.2017.00238.

Bergsma, D. P., Elshout, J. A., van der Wildt, G. J., van den Berg, A. V. (2012). Transfer effects of training-induced visual field recovery in patients with chronic stroke. Top Stroke Rehabilitation 19(3), 212-225.

Bergsma, D. P., van der Wildt, G. J. (2008). Properties of the regained visual field after visual detection training of hemianopsia patients. Restorative Neurology and Neuroscience, 26(4-5), 365-75.

Bergsma, D., Baars-Elsinga, A., Sibbel, J., Lubbers, P., Visser-Meily, A. (2014). Visual daily functioning of chronic stroke patients assessed by goal attainment scaling after visual restorative training: an explorative study. Top Stroke Rehabilitation, 21(5), 400-12.

Bergsma, D.P., van der Wildt, G. J. (2010). Visual training of cerebral blindness patients gradually enlarges the visual field. British Journal of Ophthalmology, 94(1), 88-96.

Bertini, C., Cecere, R., Làdavas, E. (2013). I am blind, but I "see" fear. Cortex, 49(4), 985-993

Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, Mourdoukoutas AP,Kronberg G, Truong D, Boggio P, Brunoni AR, Charvet L, Fregni F, Fritsch B, Gillick B, Hamilton RH, Hampstead BM, Jankord R, Kirton A, Knotkova H, Liebetanz D, Liu A, Loo C, Nitsche MA, Reis J, Richardson JD, Rotenberg A, Turkeltaub PE, Woods AJ. (2016) Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. Brain Stimul. 2016 Sep-Oct;9(5):641-61. doi: 10.1016/j.brs.2016.06.004. Epub 2016 Jun 15.

Bindman, L., Lippold, O.; Redferan, J. W. (1964): The action of brief polarizing currents on the cerebral cortex of the rat during current flow and in the producting of long-lasting after effect. The Journal of physiology 172, S. 369–382.

Bola, M., Gall, C., Moewes, C., Fedorov, A., Hinrichs, H., Sabel, B. A. (2014). Brain functional connectivity network breakdown and restoration in blindness. Neurology, 5, 83(6), 542-51.

Bowers, A. R., Keeney, K., Peli E. (2014). Randomized crossover clinical trial of real and sham peripheral prism glasses for hemianopia. JAMA Ophthalmology, 132(2), 214-22.

Brignani, Debora; Ruzzoli, Manuela; Mauri, Piercarlo; Miniussi, Carlo (2013): Is transcranial alternating current stimulation effective in modulating brain oscillations? In: PloS one 8 (2), S. e56589. DOI: 10.1371/journal.pone.0056589.

Brodtmann, A., Puce, A., Darby, D., Donnan, G. (2015). Extrastriate visual cortex reorganizes despite sequential bilateral occipital stroke: implications for vision recovery. Frontiers in Human Neuroscience, 28(9), 24.

Camilleri, R.,Pavan,A.,Ghin,F.,Battaglini,L.,Campana,G.,2014a.Improvement of uncorrected visual acuity and contrast sensitivity with perceptual learning and transcranial random noise stimulation in individuals with mild myopia. Front. Psychol.5, 1234.

Campana G, Camilleri R, Pavan A, Veronese A, Lo Giudice G. Improving visual functions in adult amblyopia with combined perceptual training and transcranial random noise stimulation (tRNS): a pilot study. Front Psychol. 2014 Dec 9;5:1402. doi: 10.3389/fpsyg.2014.01402. eCollection 2014. PubMed PMID: 25538653; PubMed Central PMCID: PMC4260493.

Cavanaugh, M. R., Zhang, R., Melnick, M. D., Das, A., Roberts, M., Tadin, D., Carrasco, M., Huxlin, K. R. (2015). Visual recovery in cortical blindness is limited by high internal noise. Journal of Vision, 15(10), 9.

Çelebisoy, M., Çelebisoy, N., Bayam, E., Köse, T. (2011). Recovery of visual-field defects after occipital lobe infarction: a perimetric study. Journal of Neurology, Neurosurgery and Psychiatry, 82(6), 695-702.

Cha, H. K., Ji, S. G., Kim, M. K., Chang, J. S. (2014). Effect of transcranial direct current stimulation of function in patients with stroke. Journal of Physical Therapy Science, 26(3), 363-5.

Chaieb L, Antal A, Paulus W. Gender-specific modulation of short-term neuroplasticity in the visual cortex induced by transcranial direct current stimulation. Vis Neurosci. 2008 Jan-Feb;25(1):77-81. doi:10.1017/S0952523808080097. PubMed PMID: 18282312.

Chokron, S., Perez, C., Obadia, M., Gaudry, I., Laloum, L., Gout, O. (2008). From blindsight to sight: cognitive rehabilitation of visual field defects. Restorative Neurology and Neuroscience, 26(4-5), 305-320.

Cooke SF: Plasticity in the human central nervous system. Brain, 2006, 129 (7): 1659–1673.

Cosman JD, Atreya PV, Woodman GF. Transient reduction of visual distraction following electrical stimulation of the prefrontal cortex. Cognition. 2015 Dec;145:73-6. doi: 10.1016/j.cognition.2015.08.010. Epub 2015 Aug 28. PubMed PMID: 26319971; PubMed Central PMCID: PMC4661068.

Costa T, Hamer RD, Nagy BV, Barboni MT, Gualtieri M, Boggio PS, Ventura DF. Transcranial direct current stimulation can selectively affect different processing channels in human visual cortex. Exp Brain Res. 2015 Apr;233(4):1213-23. doi: 10.1007/s00221-015-4199-7.

Costa TL, Gualtieri M, Barboni MT, Katayama RK, Boggio PS, Ventura DF. Contrasting effects of transcranial direct current stimulation on central and peripheral visual fields. Exp Brain Res. 2015 May;233(5):1391-7. doi: 10.1007/s00221-015-4213-0. Epub 2015 Feb 4. PubMed PMID: 25650104.

Costa TL, Nagy BV, Barboni MT, Boggio PS, Ventura DF. Transcranial direct current stimulation modulates human color discrimination in a pathway-specific manner. Front Psychiatry. 2012 Sep 12;3:78. doi: 10.3389/fpsyt.2012.00078. eCollection 2012. PubMed PMID: 22988446; PubMed Central PMCID: PMC3439847.

Cowey, A., Alexander, I., Ellison, A. (2013). Modulation of cortical excitability can speed up blindsight but not improve it. Experimental Brain Research, 224(3), 469-75.

Das, A., Huxlin, K. R. (2010). New approaches to visual rehabilitation for cortical blindness: outcomes and putative mechanisms. Neuroscientist, 16(4), 374-387

De Gelder, B., Vroomen, J., Pourtois, G., Weiskrantz, L. (1999). Non-conscious recognition of affect in the absence of striate cortex. Neuroreport, 10, 3759–3763.

de Haan, G. A., Heutink, J., Melis-Dankers, B. J., Tucha, O., Brouwer, W. H. (2014). Spontaneous recovery and treatment effects in patients with homonymous visual field defects: a meta-analysis of existing literature in terms of the ICF framework. Survey Ophthalmology, 59(1), 77-96.

Delbeke J, Oozeer M, Veraart C. Position, size and luminosity of phosphenes generated by direct optic nerve stimulation. Vision Res. 2003 Apr;43(9):1091-102.

Dilks, D., Serences, J., Rosenau, B., Yantis, S., McCloskey, M. (2007). Human adult cortical reorganization and consequent visual distortion. Journal of Neuroscience, 27(36), 9585-9594.

Ding Z, Li J, Spiegel DP, Chen Z, Chan L, Luo G, Yuan J, Deng D, Yu M, Thompson B. The effect of transcranial direct current stimulation on contrast sensitivity and visual evoked potential amplitude in adults with amblyopia. Sci Rep. 2016 Jan 14;6:19280. doi: 10.1038/srep19280.

Dobelle, W. H.; Mladejovsky, M. G. (1974): Phosphenes produced by electrical stimulation of human occipital cortex, and their application to the development of a prosthesis for the blind. In: The Journal of physiology 243 (2), S. 553–576.

Downs, S. H., Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of Epidemiology and Community Health, 52(6), 377-84.

Dundon, N. M., Bertini, C., Làdavas, E., Sabel, B. A., Gall, C. (2015). Visual rehabilitation: visual scanning, multisensory stimulation and vision restoration trainings. Frontiers Behavioral Neuroscience, 27(9), 192.

Elliott, M. A., Seifert, D., Poggel, D. A., Strasburger, H. (2015). Transient increase of intact visual field size by high-frequency narrow-band stimulation. Consciousness and Cognition, 32, 45-55.

Fedorov, A.; Jobke, S.; Bersnev, V.; Chibisova, A.; Chibisova, Y.; Gall, C.; Sabel, B. A. (2011): Restoration of vision after optic nerve lesions with noninvasive transorbital alternating current stimulation: a clinical observational study. In: Brain Stimulation 4 (4), S. 189–201. DOI: 10.1016/j.brs.2011.07.007.

Fendrich, R., Wessinger, C., Gazzaniga, M. (1992). Residual vision in a scotoma: implications for blindsight. Science, 258(5087), 1489–1491.

Fertonani, A., Pirulli, C., and Miniussi, C. (2011). Random noise stimulation improves neuroplasticity in perceptual learning. J. Neurosci. 31, 15416–15423. doi: 10.1523/JNEUROSCI.2002-11.2011

Ffytche, D., Guy, C., Zeki, S. (1995). The parallel visual motion inputs into areas V1 and V5 of human cerebral cortex. Brain, 118(6), 1375–94.

Fujikado, Takashi; Morimoto, Takeshi; Matsushita, Kenji; Shimojo, Hiroshi; Okawa, Yoshitaka; Tano, Yasuo (2006): Effect of transcorneal electrical stimulation in patients with nonarteritic ischemic optic neuropathy or traumatic optic neuropathy. In: Japanese journal of ophthalmology 50 (3), S. 266–273. DOI: 10.1007/s10384-005-0304-y.

Gall C, Lucklum J, Sabel BA, et al.: Vision- and Health-Related Quality of Life in Patients with Visual Field Loss after Postchiasmatic Lesions. Invest. Ophthalmol. Vis. Sci., 2009, 50 (6): 2765.

Gall C, Mueller I, Gudlin J, et al.: Vision- and health-related quality of life before and after vision restoration training in cerebrally damaged patients. Restor Neurol Neurosci, 2008, 26 (4-5): 341–353.

Gall C, Sabel BA: Reading performance after vision rehabilitation of subjects with homonymous visual field defects. PM R, 2012, 4 (12): 928–935.

Gall, C., Lucklum, J., Sabel, B. A., Franke, G. H. (2009). Vision- and health-related quality of life in patients with visual field loss after postchiasmatic lesions. Investigative Ophthalmology and Visual Science, 50(6), 2765-76.

Gall, C., Mueller, I., Gudlin, J., Lindig, A., Schlueter, D., Jobke, S., Franke, G. H., Sabel, B. A. (2008). Vision- and health-related quality of life before and after vision restoration training in cerebrally damaged patients. Restorative Neurology and Neuroscience, 26(4-5), 341-53.

Gall, C., Sabel, B. A. (2012) Reading performance after vision rehabilitation of subjects with homonymous visual field defects. PM&R, 4(12), 928-35.

Gall, C., Steger, B., Koehler, J. and Sabel, B.A. (2013). Evaluation of two treatment outcome prediction models for restoration of visual fields in patients with postchiasmatic visual pathway lesions. Neuropsychologia 51: 2271-2280.

Gall, Carolin; Fedorov, Anton B.; Ernst, Lisa; Borrmann, Antonia; Sabel, Bernhard A. (2010): Repetitive transorbital alternating current stimulation in optic neuropathy. In: NeuroRehabilitation 27 (4), S. 335–341. DOI: 10.3233/NRE-2010-0617.

Gall, Carolin; Schmidt, Sein; Schittkowski, Michael P.; Antal, Andrea; Ambrus, Géza Gergely; Paulus, Walter et al. (2016): Alternating Current Stimulation for Vision Restoration after Optic Nerve Damage: A Randomized Clinical Trial. In: PloS one 11 (6), S. e0156134. DOI: 10.1371/journal.pone.0156134.

Gall, Carolin; Sgorzaly, Susann; Schmidt, Sein; Brandt, Stephan; Fedorov, Anton; Sabel, Bernhard A. (2011): Noninvasive transorbital alternating current stimulation improves subjective visual functioning and vision-related quality of life in optic neuropathy. In: Brain Stimulation 4 (4), S. 175–188. DOI: 10.1016/j.brs.2011.07.003.

Goodwin, D. (2014). Homonymous hemianopia: challenges and solutions. Journal of Clinical Ophthalmology, 22(8), 1919-27.

Gray, C., French, J., Bates, D., Cartlidge, N., Venables, G., James, O. (1989). Recovery of visual fields in acute stroke: homonymous hemianopia associated with adverse prognosis. Age Ageing, 18(6), 419-421.

Grunda, T., Marsalek, P., & Sykorova, P. (2013). Homonymous hemianopia and related visual defects: Restoration of vision after a stroke. Acta neurobiologiae Experimentalis, 73(2), 237-249.

Haan GA de, Heutink J, Melis-Dankers BJ, et al.: Spontaneous recovery and treatment effects in patients with homonymous visual field defects: a meta-analysis of existing literature in terms of the ICF framework. Survey of Ophthalmology, 2014, 59 (1): 77–96.

Halko MA, Eldaief MC, Pascual-Leone A. Noninvasive brain stimulation in the study of the human visual system. J Glaucoma. 2013 Jun-Jul;22 Suppl 5:S39-41. doi: 10.1097/IJG.0b013e3182934b31. Review. PubMed PMID: 23733126; PubMed Central PMCID: PMC3786182.

Halko, M. A., Datta, A., Plow, E. B., Scaturro, J., Bikson, M., Merabet, L. B. (2011). Neuroplastic changes following rehabilitative training correlate with regional electrical field induced with tDCS. Neuroimage, 57, 885-891.

Han L, Law-Gibson D, Reding M: Key neurological impairments influence function-related group outcomes after stroke. Stroke, 2002, 33 (7): 1920–1924.

Henriksson L, Raninen A, Nasanen R, et al.: Training-induced cortical representation of a hemianopic hemifield. Journal of Neurology, Neurosurgery & Psychiatry, 2007, 78 (1): 74–81.

Herpich, F., Melnick, M., Huxlin, K., Tadin, D., Agosta, S., Battelli, L. (2015). Transcranial Random Noise Stimulation Enhances Visual Learning In Healthy Adults. Journal of Vision, 15(12), 40.

Hier, D., Mondlock, J., Caplan, L. (1983). Behavioral abnormalities after right hemisphere stroke. Neurology, 33(3), 337–344.

Huxlin, K. R., Martin, T., Kelly, K., Riley, M., Friedman, D. I., Burgin, W. S., Hayhoe, M. (2009). Perceptual relearning of complex visual motion after V1 damage in humans. Journal of Neuroscience. 29(13), 3981-3991.

Inomata, Koichi; Shinoda, Kei; Ohde, Hisao; Tsunoda, Kazushige; Hanazono, Gen; Kimura, Itaru et al. (2007): Transcorneal electrical stimulation of retina to treat longstanding retinal artery occlusion. In: Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 245 (12), S. 1773–1780. DOI: 10.1007/s00417-007-0610-9.

Ishiai, S., Furukawa, T., Tsukagoshi, H. (1987). Eye-fixation patterns in homonymous hemianopia and unilateral spatial neglect. Neuropsychologia, 25(4), 675-679.

Jobke, S., Kasten, E., Sabel, B. A. (2009). Vision restoration through extrastriate stimulation in patients with visual field defects: a double-blind and randomized experimental study. Neurorehabilitation and Neural Repair, 23(3), 246-255.

Jongbloed L: Prediction of function after stroke: a critical review. Stroke, 1986, 17 (4): 765–776.

Julkunen, L., Tenovuo, O., Jääskeläinen, S., Hämäläinen, H. (2003). Rehabilitation of chronic post-stroke visual field defect with computer-assisted training: a clinical and neurophysiological study. Restorative Neurology and Neuroscience, 21(1-2), 19-28.

Julkunen, L., Tenovuo, O., Vorobyev, V., Hiltunen, J., Teräs, M., Jääskeläinen, S. K., Hämäläinen, H. (2006). Functional brain imaging, clinical and neurophysiological outcome of visual rehabilitation in a chronic stroke patient. Restorative Neurology and Neuroscience, 24(2), 123-32.

Kanai, Ryota; Chaieb, Leila; Antal, Andrea; Walsh, Vincent; Paulus, Walter (2008): Frequency-dependent electrical stimulation of the visual cortex. In: Current biology : CB 18 (23), S. 1839–1843. DOI: 10.1016/j.cub.2008.10.027.

Kanai, Ryota; Paulus, Walter; Walsh, Vincent (2010): Transcranial alternating current stimulation (tACS) modulates cortical excitability as assessed by TMS-induced phosphene thresholds. In: Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 121 (9), S. 1551–1554. DOI: 10.1016/j.clinph.2010.03.022.

Kar, Kohitij; Krekelberg, Bart (2012): Transcranial electrical stimulation over visual cortex evokes phosphenes with a retinal origin. In: Journal of neurophysiology 108 (8), S. 2173–2178. DOI: 10.1152/jn.00505.2012.

Kar, Kohitij; Krekelberg, Bart (2014): Transcranial alternating current stimulation attenuates visual motion adaptation. In: The Journal of neuroscience : the official journal of the Society for Neuroscience 34 (21), S. 7334–7340. DOI: 10.1523/JNEUROSCI.5248-13.2014.

Kara Rogers (2010) The Eye: The Physiology of Human Perception, Britannica Educational publishing, ISBN-13: 978-1615301164

Kasten E, Poggel DA, Müller-Oehring E, et al.: Restoration of vision II: residual functions and training-induced visual field enlargement in brain-damaged patients. Restor Neurol Neurosci, 1999, 15 (2-3): 273–287.

Kasten E, Poggel DA, Sabel BA: Computer-based training of stimulus detection improves color and simple pattern recognition in the defective field of hemianopic subjects. Journal of Cognitive Neuroscience, 2000, 12 (6): 1001–1012.

Kasten E, Sabel BA: Visual field enlargement after computer training in brain-damaged patients with homonymous deficits: an open pilot trial. Restor Neurol Neurosci, 1995, 8 (3): 113–127.

Kasten E, Wüst S, Behrens-Baumann W, et al.: Computer-based training for the treatment of partial blindness. Nat Med, 1998, 4 (9): 1083–1087.

Kasten, E., Bunzenthal, U., Müller-Oehring, E. M., Mueller, I., Sabel, B. A. (2007). Vision restoration therapy does not benefit from costimulation: A pilot study. Journal of clinical experimental neuropsychology 29(6), 569-584.

Kasten, E., Bunzenthal, U., Sabel, B. A. (2006). Visual field recovery after vision restoration therapy (VRT) is independent of eye movements: an eye tracker study. Behavioural Brain Research, 175(1), 18-26.

Kasten, E., Müller-Oehring, E., Sabel, B. A. (2001). Stability of visual field enlargements following computer-based restitution training -- results of a follow-up. Journal of Clinical and Experimental Neuropsychology, 23(3), 297-305.

Kasten, E., Poggel, D. A., Sabel, B. A. (2000). Computer-based training of stimulus detection improves color and simple pattern recognition in the defective field of hemianopic subjects. Journal of Cognitive Neuroscience, 12(6), 1001-12.

Kasten, E., Sabel, B. A. (1995). Visual field enlargement after computer training in brain-damaged patients with homonymous deficits: an open pilot trial. Restorative Neurology and Neuroscience, 8(3), 113-27.

Kasten, E., Wuest, S., Sabel, B. A. (1998). Residual vision in transition zones in patients with cerebral blindness. Journal of Clinical and Experimental Neuropsychology, 20(5), 581-98.

Kasten, E., Wüst, S., Behrens-Baumann, W., Sabel, B. A. (1998). Computer-based training for the treatment of partial blindness. Nature Medicine 4, 1083-1087.

Kerkhoff, G. (1999). Restorative and compensatory therapy approaches in cerebral blindness - a review. Restorative Neurology and neuroscience, 15(2-3), 255-271.

Kerkhoff, G., Münßinger, U., Haaf, E., Eberle-Strauss, G., Stögerer, E. (1992). Rehabilitation of homonymous scotomata in patients with postgeniculate damage of the visual system: saccadic compensation training. Restorative Neurology and Neuroscience, 4(4), 245-254.

Kerkhoff, G., Münssinger, U., Meier, E. (1994). Neurovisual rehabilitation in cerebral blindness. Archives of Neurology, 51(5), 474-481.

Kim KU, Kim SH, An TG. Effect of transcranial direct current stimulation on visual perception function and performance capability of activities of daily living in stroke patients. (2016) J Phys Ther Sci. Sep;28(9):2572-2575.

Kinsbourne M. (1977) Hemi-neglect and hemisphere rivalry. Adv Neurol. ;18:41-9.

Kraft A, Roehmel J, Olma MC, Schmidt S, Irlbacher K, Brandt SA.(2010) Transcranial direct current stimulation effects visual perception measured by threshold perimetry. Exp Brain Res. Dec;207(3-4):283-90. doi: 10.1007/s00221-010-2453-6.

Kraft, A., Roehmel, J., Olma, M. C., Schmidt, S., Irlbacher, K., Brandt, S. A. (2010). Transcranial direct current stimulation affects visual perception measured by threshold perimetry. Experimental Brain Research, 207(3-4), 283-90.

Kuo, Min-Fang; Paulus, Walter; Nitsche, Michael A. (2014): Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases. In: NeuroImage 85, S. 948–960. DOI: 10.1016/j.neuroimage.2013.05.117.

Kurimoto, Takuji; Shinichirou Oono; Kashimoto, Ryousuke; Tagami, Yuichi; Okamoto, Norio; Osamu Mimura (2011): Transcorneal electrical stimulation improves visual function in eyes with branch retinal artery occlusion. In: OPTH, S. 397. DOI: 10.2147/OPTH.S17751.

Laczó, Bence; Antal, Andrea; Niebergall, Robert; Treue, Stefan; Paulus, Walter (2012): Transcranial alternating stimulation in a high gamma frequency range applied over V1 improves contrast perception but does not modulate spatial attention. In: Brain Stimulation 5 (4), S. 484–491. DOI: 10.1016/j.brs.2011.08.008.

Lane, A. R, Smith, D. T., Schenk, T. (2008). Clinical treatment options for patients with homonymous visual field defects. Journal of Clinical Ophthalmology, 2(1), 93-102.

Lang N, Siebner HR, Chadaide Z, Boros K, Nitsche MA, Rothwell JC, Paulus W, Antal A. Bidirectional modulation of primary visual cortex excitability: a combined tDCS and rTMS study. Invest Ophthalmol Vis Sci. 2007 Dec;48(12):5782-7. PubMed PMID: 18055832.

Leclercq M, Zimmermann P: Applied neuropsychology of attention: Theory, diagnosis and rehabilitation. Hove: Psychology Press, Taylor & Francis Group, 2013.

Leff, A. P., Behrmann, M. (2008). Treatment of reading impairment after stroke. Current Opinion in Neurology, 21(6), 644-648

Lolas, F. (1977): Brain polarization: behavioral and therapeutic effects. In: Biological psychiatry 12 (1), S. 37–47.

Mahmoudi H, Haghighi AB, Petramfar P, et al.: Transcranial direct current stimulation: electrode montage in stroke. Disability and Rehabilitation, 2011, 33 (15-16): 1383–1388.

Marshall RS, Ferrera JJ, Barnes A, et al.: Brain Activity Associated With Stimulation Therapy of the Visual Borderzone in Hemianopic Stroke Patients. Neurorehabilitation and Neural Repair, 2007, 22 (2): 136–144.

Marshall, RS., Chmayssani, M., O'Brien, K. A., Handy, C., Greenstein, V. C. (2010). Visual field expansion after visual restoration therapy. Clinical Rehabilitation, 24(11), 1027-1035.

Marshall, R. S., Ferrera, J. J., Barnes, A., Xian Zhang, O'Brien, K. A., Chmayssani, M., Hirsch, J., Lazar, R. M. (2008). Brain activity associated with stimulation therapy of the visual borderzone in hemianopic stroke patients. Neurorehabilitation and Neural Repair, 22(2), 136-144.

Matteo BM, Viganò B, Cerri CG, et al.: Visual field restorative rehabilitation after brain injury. J Vis, 2016, 16 (9): 11.

Meienberg, O., Zangemeister, W. H., Rosenberg, M., Hoyt, W. F., Stark, L. (1981). Saccadic eye movement strategies in patients with homonymous hemianopia. Annals of Neurology, 9(6), 537-44.

Meinzer, M., Darkow, R., Lindenberg, R, Flöel, A. (2016). Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia. Brain, 139(4), 1152-63.

Melnick, M. D., Tadin, D., Huxlin, K. R (2016). Relearning to See in Cortical Blindness. Neuroscientist, 22(2), 199-212.

Mödden, C., Behrens, M., Damke, I., Eilers, N., Kastrup, A., Hildebrandt, H. (2012). A randomized controlled trial comparing 2 interventions for visual field loss with standard occupational therapy during in patient stroke rehabilitation. Neurorehabilitation and Neural Repair, 26(5), 463-469.

Morimoto, Takeshi; Fukui, Takehiro; Matsushita, Kenji; Okawa, Yoshitaka; Shimojyo, Hiroshi; Kusaka, Shunji et al. (2006): Evaluation of residual retinal function by pupillary constrictions and phosphenes using transcorneal electrical stimulation in patients with retinal degeneration. In: Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 244 (10), S. 1283–1292. DOI: 10.1007/s00417-006-0260-3.

Mueller, I., Gall, C., Kasten, E., Sabel, B. A. (2008). Long-term learning of visual functions in patients after brain damage. Behavioural Brain Research, 191(1), 32-42.

Mueller, I., Mast, H., Sabel, B. A. (2007). Recovery of visual field defects: a large clinical observational study using vision restoration therapy. Restorative Neurology and Neuroscience, 25(5-6), 563-572.

Mueller, I., Poggel, D.A., Kenkel, S., Kasten, E., Sabel, B. A. (2003). Vision restoration therapy after brain damage: Subjective improvements of activities of daily life and their relationship to visual field enlargements. Visual Impairment Research, 5(3), 157–178

Naycheva, Lubka; Schatz, Andreas; Röck, Tobias; Willmann, Gabriel; Messias, André; Bartz-Schmidt, Karl Ulrich et al. (2012): Phosphene thresholds elicited by transcorneal electrical stimulation in healthy subjects and patients with retinal diseases. In: Investigative ophthalmology & visual science 53 (12), S. 7440–7448. DOI: 10.1167/iovs.12-9612.

Naycheva, Lubka; Schatz, Andreas; Willmann, Gabriel; Bartz-Schmidt, Karl Ulrich; Zrenner, Eberhart; Röck, Tobias; Gekeler, Florian (2013): Transcorneal Electrical Stimulation in Patients with Retinal Artery Occlusion: A Prospective, Randomized, Sham-Controlled Pilot Study. In: Ophthalmol Ther 2 (1), S. 25–39. DOI: 10.1007/s40123-013-0012-5.

Nitsche, Michael A.; Cohen, Leonardo G.; Wassermann, Eric M.; Priori, Alberto; Lang, Nicolas; Antal, Andrea et al. (2008): Transcranial direct current stimulation: State of the art 2008. In: Brain Stimulation 1 (3), S. 206–223. DOI: 10.1016/j.brs.2008.06.004.

Nitsche, Michael A.; Nitsche, Maren S.; Klein, Cornelia C.; Tergau, Frithjof; Rothwell, John C.; Paulus, Walter (2003): Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. In: Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 114 (4), S. 600–604.

Olma MC, Dargie RA, Behrens JR, et al.: Long-Term Effects of Serial Anodal tDCS on Motion Perception in Subjects with Occipital Stroke Measured in the Unaffected Visual Hemifield. Front. Hum. Neurosci., 2013, 7.

Olma, M. C., Dargie, R. A., Behrens, J. R., Kraft, A., Irlbacher, K., Fahle, M., Brandt, S. A. (2013). Long-Term Effects of Serial Anodal tDCS on Motion Perception in Subjects with Occipital Stroke Measured in the Unaffected Visual Hemifield. Frontiers in Human Neuroscience 24, 7, 314.

Olma, M.C., Kraft, A., Roehmel, J., Irlbacher, K., Brandt, S. A. (2011). Excitability changes in the visual cortex quantified with signal detection analysis. Restorative Neurology and Neuroscience, 29(6), 453-461.

Ozeki, Naoki; Shinoda, Kei; Ohde, Hisao; Ishida, Susumu; Tsubota, Kazuo (2013): Improvement of visual acuity after transcorneal electrical stimulation in case of Best vitelliform macular dystrophy. In: Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 251 (7), S. 1867–1870. DOI: 10.1007/s00417-013-2341-4.

Pambakian A, Currie J, Kennard C: Rehabilitation strategies for patients with homonymous visual field defects. J Neuroophthalmol, 2005, 25 (2): 136–142.

Pambakian, A. L., Wooding, D. S., Patel, N., Morland A. B., Kennard, C., Mannan, S. K. (2000). Scanning the visual world: a study of patients with homonymous hemianopia. Journal Neurology Neurosurgery and Psychiatry, 69(6), 751-9.

Pambakian, A., Currie, J., Kennard, C. (2005). Rehabilitation strategies for patients with homonymous visual field defects. Journal of Neuro-ophthalmology, 25(2), 136-142.

Paulus, Walter (2010): On the difficulties of separating retinal from cortical origins of phosphenes when using transcranial alternating current stimulation (tACS). In: Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 121 (7), S. 987–991. DOI: 10.1016/j.clinph.2010.01.029.

Pegna, A. J., Khateb, A., Lazeyras, F., Seghier, M. L. (2005). Discriminating emotional faces without primary visual cortices involves the right amygdala. Nature Neuroscience, 8(1), 24-25.

Pirulli, C., Fertonani, A., and Miniussi, C. (2013). The role of timing in the induction of neuromodulation in perceptual learning by transcranial electric stimulation. Brain stimul. 6, 683–689. doi: 10.1016/j.brs.2012.12.005

Pleger, B., Foerster, A. F., Widdig, W., Henschel, M., Nicolas, V., Jansen, A., Frank, A., Knecht, S., Schwenkreis, P., Tegenthoff, M. (2003). Functional magnetic resonance imaging mirrors recovery of visual perception after repetitive tachistoscopic stimulation in patients with partial cortical blindness. Neuroscience Letters, 2, 335(3), 192-6.

Plow, E. B., Obretenova, S. N., Halko, M. A., Kenkel, S., Jackson, M. L., Pascual-Leone, A., Merabet, L. B. (2011). Combining visual rehabilitative training and noninvasive brain stimulation to enhance visual function in patients with hemianopia: a comparative case study. PM&R Journal, 3(9), 825-835.

Plow, E. B., Obretenova, S. N., Jackson, M. L., Merabet, L. B. (2012a). Temporal profile of functional visual rehabilitative outcomes modulated by transcranial direct current stimulation. Neuromodulation, 15(4), 367-73.

Plow,E. B., Obretenova, S. N., Fregni, F., Pascual-Leone, A., Merabet, L. B. (2012b) Comparison of visual field training for hemianopia with active versus sham transcranial direct cortical stimulation. Neurorehabilitation and Neural Repair, 26(6), 616-626.

Poggel, D. A., Kasten, E., Müller-Oehring, E. M., Bunzenthal, U., Sabel B. A. (2006). Improving residual vision by attentional cueing in patients with brain lesions. Brain Research, 1097(1), 142-148.

Poggel, D. A., Kasten, E., Sabel, B. A. (2004). Attentional cueing improves vision restoration therapy in patients with visual field defects. Neurology, 63(11), 2069-2076.

Poggel, D. A., Mueller, I., Kasten, E., Bunzenthal, U., Sabel B. A. (2010). Subjective and objective outcome measures of computer-based vision restoration training. NeuroRehabilitation, 27(2), 173-187.

Poggel, D. A., Mueller, I., Kasten, E., Sabel, B. A. (2008). Multifactorial predictors and outcome variables of vision restoration training in patients with post-geniculate visual field loss. Restorative Neurology and Neuroscience, 26(4-5), 321-339.

Poggel, D. A., Treutwein, B., Sabel, B. A., Strasburger, H. (2015). A matter of time: improvement of visual temporal processing during training-induced restoration of light detection performance. Frontiers in Psychology, 6, 22.

Pollock A, Hazelton C, Henderson CA, et al.: Cochrane Database of Systematic Reviews, 1996, 44 Suppl 2 (5): A312.

Pollock, A., Hazelton, C., Henderson, C. A., Angilley, J., Dhillon, B., Langhorne, P., Livingstone, K., Munro, FA., Orr, H., Rowe, F., Shahani U. (2012). Interventions for visual field defects in patients with stroke. Stroke, 43(4), 37-38.

Polonara, G., Salvolini, S., Fabri, M., Mascioli, G., Cavola, G., Neri, P., Mariotti, C., Giovannini, A., Salvolini, U. (2011). Unilateral visual loss due to ischaemic injury in the right calcarine region: a functional magnetic resonance imaging and diffusion tension imaging follow-up study. Internaional Journal of Ophthalmology, 31(2), 129-134

Pommerenke, K., Markowitsch, H. (1989). Rehabilitation training of homonymous visual field defects in patients with postgeniculate damage of the visual system. Restorative Neurology and Neuroscience, 1(1), 47-63.

Pouget, M. C., Lévy-Bencheton, D., Prost, M., Tilikete, C., Husain, M., Jacquin-Courtois, S. (2012). Acquired visual field defects rehabilitation: critical review and perspectives. Annals of Physical and Rehabilitation Medicine, 55(1), 53-74.

Raco, Valerio; Bauer, Robert; Olenik, Mark; Brkic, Diandra; Gharabaghi, Alireza (2014): Neurosensory effects of transcranial alternating current stimulation. In: Brain Stimulation 7 (6), S. 823–831. DOI: 10.1016/j.brs.2014.08.005.

Raemaekers M, Bergsma DP, van Wezel,R. J. A., et al.: Effects of Vision Restoration Training on Early Visual Cortex in Patients With Cerebral Blindness Investigated With Functional Magnetic Resonance Imaging. Journal of Neurophysiology, 2011, 105 (2): 872–882.

Raninen, A., Vanni, S., Hyvärinen, L., Näsänen, R. (2007). Temporal sensitivity in a hemianopic visual field can be improved by long-term training using flicker stimulation. Journal of Neurology, Neurosurgery and Psychiatry, 78(1), 66-73.

Reinhard, J., Schreiber, A., Schiefer, U., Kasten, E., Sabel, B. A., Kenkel, S., Vonthein, R., Trauzettel-Klosinski, S. (2005). Does visual restitution training change absolute homonymous visual field defects? A fundus controlled study. British Journal of Ophthalmology, 89(1), 30-35.

Reinhart RM, Cosman JD, Fukuda K, Woodman GF. Using transcranial direct-current stimulation (tDCS) to understand cognitive processing. Atten Percept Psychophys. 2017 Jan;79(1):3-23. doi: 10.3758/s13414-016-1224-2. Review. PubMed PMID: 27804033; PubMed Central PMCID: PMC5539401.

Reinhart RM, Woodman GF. The surprising temporal specificity of direct-current stimulation. Trends Neurosci. 2015 Aug;38(8):459-61. doi: 10.1016/j.tins.2015.05.009. Epub 2015 Jun 17.

Reinhart RM, Xiao W, McClenahan LJ, Woodman GF. Electrical Stimulation of Visual Cortex Can Immediately Improve Spatial Vision. Curr Biol. 2016 Jul 25;26(14):1867-72. doi: 10.1016/j.cub.2016.05.019. Epub 2016 Jun 30. PubMed

Richard B, Johnson AP, Thompson B, Hansen BC. The Effects of tDCS Across the Spatial Frequencies and Orientations that Comprise the Contrast Sensitivity Function. Front Psychol. 2015 Nov 27;6:1784. doi: 10.3389/fpsyg.2015.01784. eCollection 2015. PubMed PMID: 26640448; PubMed Central PMCID: PMC4661264.

Ro, T., Rafal, R. (2006). Visual restoration in cortical blindness: insights from natural and TMS-induced blindsight. Neuropsychological Rehabilitation, 16(4), 377-96.

Romano, J. G. (2009). Progress in rehabilitation of hemianopic visual field defects. Cerebrovascolar Disease, 27 (1), 187-90.

Romano, J. G., Schulz, P., Kenkel, S., Todd, D. P. (2008). Visual field changes after a rehabilitation intervention: vision restoration therapy. Journal of Neurological Sciences, 273(1-2), 70-74.

Roth, T., Sokolov, A., Messias, A., Roth, P., Weller, M., Trauzettel-Klosinski, S. (2009). Comparing explorative saccade and flicker training in hemianopia: a randomized controlled study. Neurology, 72(4), 324-331.

Rowe F, Brand D, Jackson CA, et al.: Visual impairment following stroke: do stroke patients require vision assessment? Age Ageing, 2009, 38 (2): 188–193.

Rowe, F., Brand, D., Jackson, C., Price, A., Walker, L., Harrison, S., Eccleston, C., Scott, C., Akerman, N., Dodridge, C., Howard, C., Shipman, T., Sperring, U., MacDiarmid, S., Freeman, C. (2009). Visual impairment following stroke: do stroke patients require vision assessment? Age and Ageing, 38(2), 188–193.

Russo C, Souza Carneiro MI, Bolognini N, Fregni F. (2017) Safety Review of Transcranial Direct Current Stimulation in Stroke. Neuromodulation. Apr;20(3):215-222. doi: 10.1111/ner.12574. Epub 2017 Feb 21.

Sabel BA, Henrich-Noack P, Fedorov A, et al.: Vision restoration after brain and retina damage: the "residual vision activation theory". Prog Brain Res, 2011, 192: 199–262.

Sabel BA, Kasten E: Restoration of vision by training of residual functions. Curr Opin Ophthalmol, 2000, 11 (6): 430–436.

Sabel BA, Kenkel S, Kasten E: Vision restoration therapy (VRT) efficacy as assessed by comparative perimetric analysis and subjective questionnaires. Restor Neurol Neurosci, 2004, 22 (6): 399–420.

Sabel, B. A., Henrich-Noack, P., Fedorov, A., Gall, C. (2011). Vision restoration after brain and retina damage: the "residual vision activation theory". Progress in Brain Research, 192, 199-262.

Sabel, B. A., Kasten, E. (2000). Restoration of vision by training of residual functions. Current Opinion Ophthalmology, 11, (6), 430-6.

Sabel, B. A., Kasten, E., Kreutz, M. R. (1997). Recovery of vision after partial visual system injury as a model of postlesion neuroplasticity. Advances in Neurology, 73, 251-76.

Sabel, B. A., Kenkel, S., Kasten, E. (2004). Vision restoration therapy (VRT) efficacy as assessed by comparative perimetric analysis and subjective questionnaires. Restorative Neurology and Neuroscience, 22(6), 399-420.

Sabel, B. A., Kruse, R., Wolf, F., Guenther, T. (2013). Local topographic influences on vision restoration hot spots after brain damage. Restorative Neurology and Neuroscience, 31(6), 787-803.

Sabel, B.A., Fedorov, A., Henrich-Noack, P. and Gall, C. (2011). Vision restoration after brain damage: The “Residual Vision Activation Theory”. Progress in Brain Research 192: 199-262.

Sabel, Bernhard A.; Fedorov, Anton B.; Naue, Nicole; Borrmann, Antonia; Herrmann, Christoph; Gall, Carolin (2011): Non-invasive alternating current stimulation improves vision in optic neuropathy. In: Restorative neurology and neuroscience 29 (6), S. 493–505. DOI: 10.3233/RNN-2011-0624.

Sahraie, A., Macleod, M. J., Trevethan, C. T., Robson, S. E., Olson, J. A., Callaghan, P., Yip B. (2010). Improved detection following Neuro-Eye Therapy in patients with post-geniculate brain damage. Experimental Brain Research, 206(1), 25-34.

Sahraie, A., Trevethan, C. T., MacLeod, M. J., Murray, A. D., Olson, J. A., Weiskrantz, L. (2006). Increased sensitivity after repeated stimulation of residual spatial channels in blindsight. Proceedings of the National Academy of Sciences, 103(40), 14971-14976.

Sahraie, A., Trevethan, C. T., Macleod, M. J., Weiskrantz, L., Hunt, A. R. (2013). The continuum of detection and awareness of visual stimuli within the blindfield: from blindsight to the sighted-sight. Investigative Ophthalmology and Visual Science, 54(5), 3579-85.

Sanders, M. D., Warrington, E. K., Marshall, J., & Weiskrantz, L. (1974). ‘Blindsight’: Vision in a field defect. Lancet, 1, 707–708.

Schatz, Andreas; Pach, Johanna; Gosheva, Mariya; Naycheva, Lubka; Willmann, Gabriel; Wilhelm, Barbara et al. (2017): Transcorneal Electrical Stimulation for Patients With Retinitis Pigmentosa: A Prospective, Randomized, Sham-Controlled Follow-up Study Over 1 Year. In: Investigative ophthalmology & visual science 58 (1), S. 257–269. DOI: 10.1167/iovs.16-19906.

Schatz, Andreas; Röck, Tobias; Naycheva, Lubka; Willmann, Gabriel; Wilhelm, Barbara; Peters, Tobias et al. (2011): Transcorneal electrical stimulation for patients with retinitis pigmentosa: a prospective, randomized, sham-controlled exploratory study. In: Investigative ophthalmology & visual science 52 (7), S. 4485–4496. DOI: 10.1167/iovs.10-6932.

Schmidt, Sein; Mante, Alf; Rönnefarth, Maria; Fleischmann, Robert; Gall, Carolin; Brandt, Stephan A. (2013): Progressive enhancement of alpha activity and visual function in patients with optic neuropathy: A two-week repeated session alternating current stimulation study. In: Brain Stimulation 6 (1), S. 87–93. DOI: 10.1016/j.brs.2012.03.008.

Schmielau, F., Wong, E. K. (2007). Recovery of visual fields in brain-lesioned patients by reaction perimetry treatment. Journal of NeuroEngineering and Rehabilitation, 4-31.

Schofield, T. M., Leff, A. P. (2009). Rehabilitation of hemianopia. Current Opinion in Neurology, 22(1), 36-40.

Schreiber, A., Vonthein, R., Reinhard, J., Trauzettel-Klosinski, S., Connert, C., Schiefer U. (2006). Effect of visual restitution training on absolute homonymous scotomas. Neurology, 67(1), 143-145.

Schuett, S. (2009). The rehabilitation of hemianopic dyslexia. Nature Reviews Neurology, 5(8), 427-437.

Schutter, Dennis J L G; Hortensius, Ruud (2010): Retinal origin of phosphenes to transcranial alternating current stimulation. In: Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 121 (7), S. 1080–1084. DOI: 10.1016/j.clinph.2009.10.038.

Sehic, Amer; Guo, Shuai; Cho, Kin-Sang; Corraya, Rima M.; Chen, Dong F.; Utheim, Tor P. (2016): Electrical Stimulation as a Means for Improving Vision. In: The American journal of pathology 186 (11), S. 2783–2797. DOI: 10.1016/j.ajpath.2016.07.017.

Shinoda, Kei; Imamura, Yutaka; Matsuda, Sayaka; Seki, Maiko; Uchida, Atsuro; Grossman, Terry; Tsubota, Kazuo (2008): Transcutaneous electrical retinal stimulation therapy for age-related macular degeneration. In: The open ophthalmology journal 2, S. 132–136. DOI: 10.2174/1874364100802010132.

Spiegel DP, Byblow WD, Hess RF, Thompson B. Anodal transcranial direct current stimulation transiently improves contrast sensitivity and normalizes visual cortex activation in individuals with amblyopia. Neurorehabil Neural Repair. 2013 Oct;27(8):760-9. doi: 10.1177/1545968313491006. Epub 2013 Jun 17.

Spiegel DP, Hansen BC, Byblow WD, Thompson B. Anodal transcranial direct current stimulation reduces psychophysically measured surround suppression in the human visual cortex. PLoS One. 2012;7(5):e36220. doi: 10.1371/journal.pone.0036220. Epub 2012 May 1. PubMed PMID: 22563485; PubMed Central PMCID: PMC3341359.

Spiegel DP, Li J, Hess RF, Byblow WD, Deng D, Yu M, Thompson B. Transcranial direct current stimulation enhances recovery of stereopsis in adults with amblyopia. Neurotherapeutics. 2013 Oct;10(4):831-9. doi: 10.1007/s13311-013-0200-y.

Strigaro G, Mayer I, Chen JC, Cantello R, Rothwell JC. Transcranial Direct Current Stimulation Effects on Single and Paired Flash Visual Evoked Potentials. (2014) Clin EEG Neurosci. 2015 Jul;46(3):208-13. doi: 0.1177/1550059414539481.

Terhune DB, Tai S, Cowey A, Popescu T, Cohen Kadosh R. Enhanced cortical excitability in grapheme-color synesthesia and its modulation. Curr Biol. 2011 Dec 6;21(23):2006-9. doi: 10.1016/j.cub.2011.10.032. Epub 2011 Nov 17. PubMed PMID: 22100060; PubMed Central PMCID: PMC3242051.

Terhune, Devin B.; Song, Seoho M.; Cohen Kadosh, Roi (2015): Transcranial alternating current stimulation reveals atypical 40 Hz phosphene thresholds in synaesthesia. In: Cortex; a journal devoted to the study of the nervous system and behavior 63, S. 267–270. DOI: 10.1016/j.cortex.2014.09.006.

Trauzettel-Klosinski, S. (2010). Rehabilitation for visual disorders. Journal of Neuroophthalmology, 30(1), 73-84.

Turco, Simona; Albamonte, Emilio; Ricci, Daniela; Fortini, Stefania; Amore, Filippo Maria (2015): Bernhard Sabel and 'Residual Vision Activation Theory': a History Spanning Three Decades. In: Multisensory research 28 (3-4), S. 309–330.

Turi, Zs; Ambrus, G. G.; Janacsek, K.; Emmert, K.; Hahn, L.; Paulus, W.; Antal, A. (2013): Both the cutaneous sensation and phosphene perception are modulated in a frequency-specific manner during transcranial alternating current stimulation. In: Restorative neurology and neuroscience 31 (3), S. 275–285. DOI: 10.3233/RNN-120297.

Vaina, L. M., Soloviev, S., Calabro, F. J., Buonanno, F., Passingham, R., Cowey, A. (2014). Reorganization of retinotopic maps after occipital lobe infarction. Journal of Cognitive Neuroscience, 26(6), 1266-82.

van der Wildt, G. J., Bergsma, D. P. (1997). Visual field enlargement by neuropsychological training of a hemianopsia patient. Documenta Ophthalmologica, 93(4), 277-292.

Vanni, S., Raninen, A., Näsänen, R., Tanskanen, T., Hyvärinen, L. (2001). Dynamics of cortical activation in a hemianopic patient. Neuroreport, 26, 12(4), 861-5.

Wang, M. K. (2003). Reading with a right homonimous hemianopia. Lancet, 361(9363), 1138.

Weiskrantz, L., Harlow, A., Barbur, J. (1991). Factors affecting visual sensitivity in a hemianopic subject. Brain, 5, 2269-2282.

World Health Organization (WHO) (2004). International classification of functioning, disability and health ICF. World Health Organization, Geneva.

Wüst, S., Kasten, E., Sabel, B. A. (2002). Blindsight after optic nerve injury indicates functionality of spared fibers. Journal of Cognitive Neuroscience, 15, 14(2), 243-53.

Xie, John; Wang, Gene-Jack; Yow, Lindy; J Cela, Carlos; Humayun, Mark S.; Weiland, James D. et al. (2011): Modeling and percept of transcorneal electrical stimulation in humans. In: IEEE transactions on bio-medical engineering 58 (7), S. 1932–1939. DOI: 10.1109/TBME.2010.2087378.

Zaehle, Tino; Rach, Stefan; Herrmann, Christoph S. (2010): Transcranial alternating current stimulation enhances individual alpha activity in human EEG. In: PloS one 5 (11), S. e13766. DOI: 10.1371/journal.pone.0013766.

Zeki, S., Ffytche, D. (1998). The Riddoch syndrome: insights into the neurobiology of conscious vision. Brain, 121(1), 25-45.

Zhang X, Kedar S, Lynn MJ, et al.: Natural history of homonymous hemianopia. Neurology, 2006, 66 (6): 901–905.

Zhang, X., Kedar, S., Lynn, M., Newman, N, Biousse, V. (2006c). Homonymous hemianopia in stroke. Journal of Neuro-ophthalmology, 26(3), 180-183.

Zhang, X., Kedar, S., Lynn, M., Newman, N., Biousse, V. (2006a). Natural history of homonymous hemianopia. Neurology, 66(6), 901-905.

Zhang, X., Kedar, S., Lynn, M., Newman, N., Biousse, V. (2006b). Homonymous hemianopias: clinical-anatomic correlations in 904 cases. Neurology. 66(6), 906-910.

Zihl, J., Von Crammon, D. (1982). Restitution of visual field in patients with damage to the geniculostriate visual pathway. Human Neurobiology, 1(1), 5-8.

Zihl, J., von Cramon, D. (1979). Restitution of visual function in patients with cerebral blindness. Journal of Neurology Neurosurgery and Psychiatry. 42(4), 312-322.

Zihl, J., von Cramon, D. (1985). Visual field recovery from scotoma in patients with postgeniculate damage. A review of 55 cases. Brain, 108(2), 335-365

Zihl, J., Werth, R. (1984). Contributions to the study of "blindsight"--I. Can stray light account for saccadic localization in patients with postgeniculate field defects?. Neuropsychologia, 22(1), 1-11.

Zihl, J., Werth, R. (1984) Contributions to the study of "blindsight"--II. The role of specific practice for saccadic localization in patients with postgeniculate visual field defects. Neuropsychologia, 22(1), 13-22.