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Visual field restorative rehabilitation after brain injury

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About 20%–30% of patients undergoing neurological rehabilitation report visual field defects, one of the most frequent of which is homonymous hemianopsia (loss of the same half of the visual field in both eyes). There is still no consensus as to whether homonymous hemianopsia is best treated in a restorative or compensatory manner. The aim of this review is to describe the effects of restorative rehabilitation, whose long-term efficacy is still being debated. We analyzed 56 articles describing the use of various techniques used to promote visual field recovery but concentrating on two approaches: "border training," which involves exercising vision at the edge of the damaged visual field, and "blindsight training," which is based on exercising unconscious perceptual functions in the mild of the blind hemifield where the scotoma is deep. Both techniques have been supported by functional imaging studies showing evidence of cortical rearrangement (plasticity) after rehabilitation. Although no formal meta-analysis was possible, the results of a semiquantitative evaluation suggested that the 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.

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 fibers 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, tumors, and, much less frequently, brain surgery, demyelinating diseases, and congenital diseases (Zhang, Kedar, Lynn, Newman, & Biousse, 2006b). About 20–30% of all of the patients admitted to

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neurorehabilitation 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; that is, they have a preserved area of central vision whose amplitude ranges from 2° to 5° (Wang, 2003).

The World Health Organization (2004) International Classification of Functioning, Disability and Health recognizes 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 3 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., 2006c), 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 10 days, and when the defect is incomplete, it is greatest in the first 48 hr and further recovery is minimal after 10 to 12 weeks (Zhang et al., 2006c). Zhang et al. (2006c) found that the possibility of spontaneous recovery during the first 6 months progressively decreases from 50–60% in the first month to 20% after 6 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 reorganization possible in other more overlapping neural networks (Kerkhoff, Münßinger, Haaf, Eberle-Strauss, & Stögerer, 1992).

A perimetry study by Çelebisoy, Çelebisoy, 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 color, and finally by stereopsis (Gray et al., 1989; Pambakian et al., 2005). 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 color 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 (Bertini, Cecere, & Làdavas, 2013; Pegna, Khateb, Lazeyras, & Seghier, 2005). Sahraie et al. (2006) distinguished two types of blindsight: type 1 characterized 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 extrastriatal cortical region (Fendrich, Wessinger, & Gazzaniga, 1992; Wüst, 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 extrastriatal/geniculate regions and subcortical structures (including the superior colliculus and the pulvinar) that reach the ipsilateral extrastriatal cortex via tectotectal pathways (Ffytche, Guy, & Zeki, 1995).

However, despite their highly disabling nature, visual field defects often remain untreated because they are underestimated by physicians or because the people affected spontaneously learn methods of compensation (Zhang et al., 2006a). 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 (Marshall, Chmayssani, O'Brien, Handy, & Greenstein, 2010; Romano, Schulz, Kenkel, & Todd, 2008), 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. Behavioral compensation, which is aimed at optimizing patients' behavior to improve their everyday functional performance. One example is explorative saccadic training (Roth et al., 2009), a form of rehabilitation that consists of increasing patients' attention toward the blind hemifield to allow them to scan space more carefully.
2. Substitutive compensation that 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 behavioral training or instrumental assistance (Schofield & Leff, 2009). On the contrary, visual field training techniques are aimed at improving 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 to help the brain reactivate visual function (Pollock et al., 2011).

Although a number of comparative studies have been carried out (Mödden et al., 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 (Dundon, Bertini, Làdavas, Sabel, & Gall, 2015; Goodwin, 2014).

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 reorganize 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 noninvasive brain stimulation (Herpich et al., 2015; Ro & Rafal, 2006), 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.

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 keywords *Rehabilitation* OR *Restoration* combined with *Visual Field* OR *Hemianopsia*. The search identified 1,290 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 (Figure 1).

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 (Kasten, Wuest, & Sabel, 1998; Schmielau & Wong, 2007);
2. blindsight training specifically targeting inside the blind hemifield (Sahraie et al., 2006); and
3. rehabilitation combined with noninvasive brain stimulation techniques such as transcranial direct current stimulation (tDCS).

Each article was analyzed by extrapolating the number of treated patients, the duration of the therapy, an assessment of the defect, the study end points, and

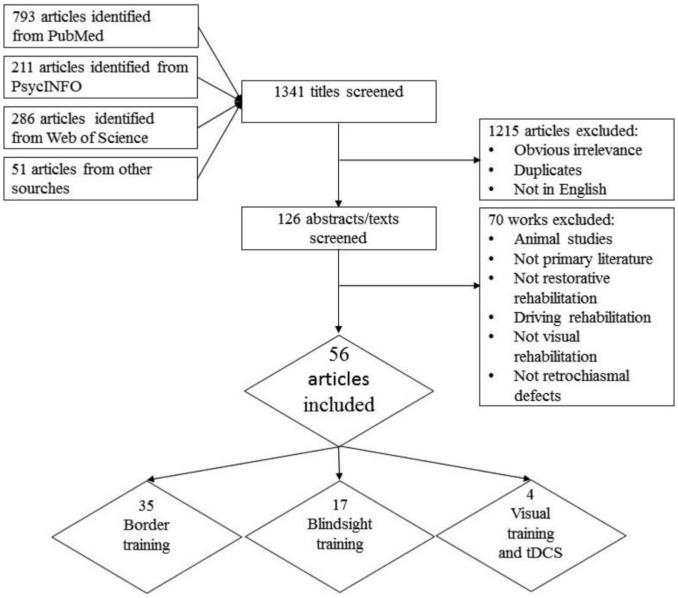

Figure 1. Flow chart of study selection.

the main results. Each endpoint 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 pretraining 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 analyzed 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 analyzed on the basis of the endpoint, the instrument used, and the results obtained, and the endpoints were then grouped into macro-categories 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 analyze a stimulus in time and space), defined as the perception of elements such as contrast, color, shape, size, frequency, and movement; the third included all of the neuropsychological endpoints 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 analyzed when the numbers allowed.

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.

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 posttreatment increase in the visual field (Zihl & von Cramon, 1979, 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.

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 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

Treatment	Code	Authors	Year	Sample size	Period of treatment
Border training	1	Zihl and von Cramon	1979	12	30 one-hour sessions
	2	Zihl and von Cramon	1985	55	80 and 120 trials daily
	3	Balliet, Blood, and Bach-y-Rita	1985	12	2–11 months
	4	Kasten and Sabel	1995	11 + 3	80–300 hr (1 hr daily)
	5	van Der Wildt and Bergsma	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 hr)
	8	Kasten et al.	2001	16 + 6	2.3 months
	9	Julkunen et al.	2003	5	33–47 hr (1 hr 3 times a week)
	10	Mueller, Poggel, Kenkel, Kasten, and Sabel	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 hr)
	15	Kasten et al.	2006	15	3 months
	16	Schreiber et al.	2006	16	6 months (1 hr daily/6 days a week)
	17	Poggel, Kasten, Müller-Oehring, Bunzenthal, and Sabel	2006	9 + 7 +7	Unspecified
	18	Kasten, Bunzenthal, Müller-Oehring, Mueller, and Sabel	2007	23	3 months (30 min twice daily)
	19	Mueller et al.	2007	302	6 months
	20	Schmielau and Wong	2007	20	8.2 months (45 min twice weekly)
	21	Bergsma and van der Wildt	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 and van der Wildt	2010	11	40 hr (1 hr daily)
	28	Marshall et al.	2010	7	3 months (twice daily)
	29	Poggel, Mueller, Kasten, Bunzenthal, and Sabel	2010	19	6 months
	30	Raemaekers et al.	2011	8	10 weeks (40 hr)
	31	Gall and Sabel	2012	11	6 months
	32	Mödden et al.	2012	15 + 15 + 15	3 weeks (fifteen 30-min sessions)
	33	Sabel et al.	2013	23	6 months
	34	Bergsma, Baars-Elsinga, Sibbel, Lubbers, and Visser-Meily	2014	12	13 weeks (1 hr/day, 5 days/week)
	35	Poggel, Treutwein, Sabel, and Strasburger	2015	9	3 months
Blindsight training	36	Vanni, Raninen, Näsänen, Tanskanen, and Hyvärinen	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	Henriksson 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 et al.	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, Elshout, van der Wildt, and van den Berg	2012	12	10 weeks (40 one-hour sessions)

Table 1. Continued.

Treatment	Code	Authors	Year	Sample size	Period of treatment
	48	Sahraie, Trevethan, Macleod, Weiskrantz, and Hunt	2013	5	30 min daily/3-month minimum
	49	Das et al.	2014	9	≥5 days/week
	50	Vaina et al.	2014	1	11 months
	51	Elliot, Seifert, Poggel, and Strasburger	2015	3	Four treatment sessions
	52	Cavanaugh et al.	2015	7	≤6 months
Training + 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 a week)
	55	Plow et al.	2012a	6 + 6	3 months (two half-hour sessions, 3 times a week)
	56	Plow et al.	2012b	4 + 4	3 months (1-hr sessions 3 days a week)

Table 1. Studies of restorative rehabilitation classified by type of treatment performed. *Notes:* The following were excluded: all transcranial direct current stimulation (tDCS) studies made in healthy subjects, study projects/protocols and studies that did not show results, articles that did not treat retrochiasmatic damage, repetitive transorbital alternating current stimulation studies, the articles of Cowey, Alexander, and Ellison (2013) and Olma et al. (2013), not doing rehabilitation but "offline tDCS."

in 8 of 13 studies, and reading abilities (tested in a total of 109 patients) significantly improved in 4 of 5 studies.

All of the studies that analyzed stimulus processing (the identification of shapes, colors, temporal, and flickers) found improvements, albeit nonsignificant, in 15 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 recorded a significant improvement.

In relation to cortical function, two studies measured visual evoked potentials, 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 has also varied widely from just a few weeks to more than 1 year, but it seems that better results are obtained using at least twice- or thrice-weekly sessions for 6 months or more (Mueller, Gall, Kasten, & Sabel, 2008).

The analyses made 3 months (Julkunen, Tenovuo, Jääskeläinen & Hämäläinen, 2003), 6 months (Schmielau & Wong, 2007), 6–12 months (Kasten & Sabel, 1995), and up to 2 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 et al. (2001) also claimed that age and gender had no effect on the stability of the improvements.

Finally, Schmielau and Wong (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.

The detection of visual field test stimuli has been evaluated in six studies involving a total of 45 patients:

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	Suprathreshold 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	Suprathreshold 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	Cancelation 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 and 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	Semistructured 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

Table 2. Continued.

CATEGORY – outcome	Assessment method	No. of articles	Results			Total No. of patients
			Significantly improved	Improved	Unchanged or worsened	
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 – Color	Peri-Color test improvement	3 (4, 7, 8)	2	1	0	46
PROCESSING – Color	Color 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

Table 2. Results of border rehabilitation studies. *Notes:* 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.

CATEGORY – Outcome	Assessment method	No. of studies	Results Significantly improved	Results Improved	Results Unchanged or worsened	Total No. of patients
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/Color	Form and color perception	1 (47)	1	0	0	12
PROCESSING – Form/Color/Pattern	Figures, pattern, and color recognition	1 (38)	0	1	0	3
PROCESSING – Static	Verbal and motor target localization	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

Table 3. Results of blindsight rehabilitation studies. *Notes:* HRP = high-resolution perimeter; TAP = Tubingen automated perimeter; ECSG = estimated cortical surface gain; MEG = magnetoencephalography; fMRI = functional magnetic resonance imaging; FUNCT/SUBJ = functional/subjective evaluation; NEI-VFQ = National Eye Institute Visual Function Questionnaire; NPSY = neuropsychology.

CATEGORY – Outcome	Assessment method	No. of studies	Results Significantly improved	Improved	Unchanged or worsened	Total No. of patients
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

Table 4. results of visual rehabilitation and tDCS studies. *Notes:* HRP = high-resolution perimeter; FUNCT/SUBJ = functional/subjective evaluation; ADLs = vision-related activities of daily living; QOL = quality of life; fMRI = funtional magnetic resonance imaging; MNREAD = Minnesota Low-Vision Reading Test.

two found a statistically significant difference, two a nonsignificant 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/color/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 estimated cortical surface gain, magnetoencephalography, 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 et al., 2010).

Transcranial direct current stimulation

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, that is, related to the rehabilitation strategy used (Plow, Obretenova, Jackson, & Merabet, 2012a). 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.

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 endpoints 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 1 month, and broadening of the visual field occurs after 3 months (Plow et al., 2012a).

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) endpoints (66.7% and 65.6%, respectively), and the majority of the stimulus processing and functional/subjective evaluation results were nonsignificantly positive (74% and 56.2%, respectively).

Excluding the macro-category of functional/subjective evaluation and eye movements (which included only two endpoints), Table 6 shows that blindsight

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%)

Table 5. Distribution of the effects of border rehabilitation by macro-category of endpoints. *Notes:* NPSY = neuropsychology; FUNCT/SUBJ = functional/subjective evaluation.

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%).

Comparison of the two tables shows that the results were distributed differently. The sample sizes of the studies with endpoints falling in the neuropsychology, functional/subjective, cortical changes, and eye movements macro-categories are too small to allow comparisons in terms of percentages, but there were enough studies with stimulus detection and processing endpoints 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 endpoints in the categories of stimulus detection and stimulus processing was statistically significant ($p < 0.0001$) and in favor 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 favor of stimulus processing. The same was true in the case of the number of significantly improved cases.

Discussion

Efficacy of restorative rehabilitation

Over the past 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 (Pollock et al., 2011; Romano et al., 2008; Sabel & Kasten, 2000; Sahraie et al., 2006). 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 test, which simply requires recognition of the light. After border rehabilitation, fMRI shows a shift in receptive fields toward greater eccentricity, and simultaneously, the 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 postrehabilitation fMRI and PET findings concordantly show widespread cortical activation. Activation of attention-related brain areas has also been observed (Julkunen et al., 2006; Marshall et al., 2008).

On the other hand, blindsight rehabilitation seems to affect signal processing, leading to a greater improvement in the detection and localization of flickering, a target or movement that mainly seems to involve the areas involved in processing visual stimuli. After

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%)

Table 6. Distribution of the effects of blindsight rehabilitation by macro-category of endpoints. *Notes:* NPSY = neuropsychology; FUNCT/SUBJ = functional/subjective evaluation.

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 reorganizing itself after it has been damaged (Romano, 2009). Sabel, Kasten, and Kreutz (1997) hypothesized 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 even if the blind field has only small, partially damaged areas of vision (Sabel et al., 2011).

Kasten et al. (1998) hypothesized 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) hypothesized that stimulating extrastriatal 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 synchronizes neuronal firing in the same areas, and, as this synchronization requires attentional activation, it leads to synaptic plasticity. It is therefore interesting that there is fMRI evidence of cortical reorganization (Bola et al., 2014; Raninen, Vanni, Hyvärinen, & Näsänen, 2007) 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 (2016) 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 (Mueller et al., 2007; Poggel, Kasten, & Sabel, 2004; Poggel, Mueller, Kasten, & Sabel, 2008), 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 (Reinhard et al., 2005; Sabel, Kenkel, & Kasten, 2004). However, many authors have now monitored eye movements and demonstrated that the postrehabilitation improvement in visual fields is due to a real gain in sensitivity rather than compensation (Gall & Sabel, 2012; Kasten, Bunzenthal, & Sabel, 2006; Marshall et al., 2008; Marshall et al., 2010; Mueller et al., 2007; Raemaekers et al., 2011).

One current subject of debate is the cost/benefit ratio of restorative rehabilitation. de Haan, Heutink, Melis-Dankers, Tucha, and Brouwer (2014) analyzed homonymous visual field defects using the components of the International Classification of Functioning, Disability, and Health 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. 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. (2016) wondered whether 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 noninvasive brain stimulation, which, when combined with rehabilitation, has led to promising results in the case of a number of focal brain lesions (aphasia, hemiplegia, etc.; Cha, Ji, Kim, & Chang, 2014; Meinzer, Darkow, Lindenberg, & Flöel, 2016), including the study of restorative therapy and tDCS-induced modulation by Plow, Obretenova, Fregni, Pascual-Leone and Merabet (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 program and/or considering whether combining the two techniques may be more functionally successful.

Keywords: homonimous hemianopia, visual field loss, stroke, training, neuroplasticity

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Appendix

Limitations

Comparing the results of different techniques may be questioned for four main reasons: (a) the difference in the number of the studies of the different types of rehabilitation, (b) the size of the study samples, (c) the absence of standardized stimulation protocols, and (d) the choice of the considered endpoints.

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 favor of blindsight rehabilitation is based on much smaller samples. Third, although it is true that the border rehabilitation method is standardized in many studies (vision restoration therapy or similar paradigms), the techniques of blindsight rehabilitation have still not been standardized. However, our detailed analysis made using a checklist designed to evaluate the methodological quality of interventional health care studies (Downs & Black, 1998) did not reveal any critical weaknesses in the studies of either technique.

Other limitations are the variability of the endpoints considered: The massive presence of the detection endpoint in border rehabilitation studies and the processing endpoint in blindsight rehabilitation studies might be a confounding factor as well as the fact that 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 multifaceted function involving various factors, such as attention and the perception of light, patterns, shapes, movement, and frequency, which justifies the use of different endpoints even though this makes comparisons more difficult.