Bernhard Sabel and ‘Residual Vision Activation Theory’: a History Spanning Three Decades

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Abstract
This review has the purpose of retracing the work of Professor Bernard Sabel and his group over the last 2–3 decades, in order to understand how they achieved formulation of the ‘Residual Vision Activation Theory’. The methodology proposed is described, from the first studies in 1995 with High Resolution Perimetry requiring a six-months training period, to the new technologies, such as repetitive transorbital Alternating Current Stimulation, that require ten days of training. Vision restoration therapy has shown improvement in visual responses irrespective of age at the training, lesion aetiology and site of lesion. The hypothesis that visual training may induce network plasticity, improving neuronal networks in cortical and subcortical areas of both hemispheres, appears to be confirmed by recent studies including observation of the cerebral activity by fMRI and EEG. However, the results are quite variable and the mechanisms that influence cerebral activity are still unclear. The residual vision activation theory has been much criticized, both for its methodology and analysis of the results, but it gave a new impulse to the research in this area, stimulating more studies on induced cerebral plasticity.

Keywords
Vision training, rehabilitation, visual field, neuroplasticity

1. Introduction

Until recently, brain damage was thought to be permanent because of the inability of neurons to reproduce. In the last 30 to 40 years, several studies have demonstrated the plasticity of brain networks, as mediated by synaptogenesis

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in response to experience and stimulation. This process allows the relearning or acquisition of abilities and appears to be age dependent. Sabel and his group have recently reported that neuroplasticity may be induced in adults with visual field deficits following spontaneous neuroplasticity. The ‘residual vision activation theory’ proposed in 2011 describes multiple factors that influence plasticity. Factors that promote plasticity include the presence of surviving neurons within, or around, the brain lesion — so-called ‘areas of residual vision’ — and the activation of unaffected extra-striatal pathways. These factors enhance the response to visual stimuli and may improve vision for use in everyday life. Factors adversely affecting plasticity include a reduction in the number of neurons, an imbalance of visual function across hemisfields that may lead to neglect of the more affected hemifield, and a disturbance in temporal processing. These factors decrease the response to visual stimuli and may further reduce useful vision (Sabel et al., 2011a).

Surviving neurons may be activated by visual experience, visual training and non-invasive electrical brain stimulation. Repetitive stimulation may induce ‘within-system plasticity’ that strengthens synaptic transmission within the partially damaged brain structures (Prilloff et al., 2007), and ‘network plasticity’ that improves neuronal networks in cortical and subcortical areas of both hemispheres. According to this hypothesis, cellular mechanisms of visual pathway restoration are similar to those that determine perceptual learning (Kasten et al., 2000). With targeted stimulation, relearning visual field pathways may occur any time after brain injury, at any age and in almost all visual field impairments, irrespective of the site (pre- or post-chiasmatic) or aetiology of the lesion. The extent of this visual field restoration would depend on the number and activation state of the ‘areas of residual vision’. Once restored, these pathways persist, even after the stimulation period, with continued use of vision (Sabel et al., 2011a).

The aim of this paper is to retrace the work that led Sabel and his group to their development of the ‘residual vision activation theory’ and to their methods of visual stimulation. We will also discuss the important criticisms of these methods and the results reported in the literature.

2. The Visual Training Method

In the 1940s, animal studies revealed that systematic training or experience can improve visual functions. However, the fundamental observation that training of visual functions can improve performance in hemianopic patients was first observed in the 1980s by Zihl et al. at the München University (Zihl et al., 1980). They found that repeated testing of the visual field border, in essentially training conditions, led to significantly increased visual field size in patients with post-chiasmatic lesions. These initial results were confirmed by subse-
quent studies (Kerkhoff et al., 1992, 1994; Pommerenke and Markowitsch, 1989).

In 1990, based on these earlier studies, a group of neuropsychologists led by Professor Sabel (Otto-von-Guericke University of Magdeburg) developed specific computer programs (Visual Restitution Training — VRT program; www.nova-vision.org) for patients with visual field deficits to evaluate whether true ‘restitution’ in the visual system was possible. In order to quantify the loss of visual function and any residual capacity they used two approaches: the Tübingen Automated Perimeter (TAP-2000) and High-Resolution Perimetry (HRP).

The TAP-2000 is a monocular static perimeter employed in routine clinical practice. This tool has been used in different studies to determine the total size of each eye’s blind area by presenting static stimuli adapted to the central threshold of visual perception at eccentricities up to 30° or 90° of visual angle. Fixation of the eye was controlled with a video camera (Kasten and Sabel, 1995) (Fig. 1).

High-Resolution Perimetry is a diagnostic computer program developed in the laboratories of the University of Magdeburg and designed to perform high-resolution qualitative perimetry of the central visual field. This tool also allows for assessment of colour and shape recognition by special subroutines. HRP consists of three programs, ‘PeriMa’, ‘PeriForm’ and ‘PeriColor’ (Kasten et al., 1997) (Fig. 1).

The ‘PeriMa’ program examines visual field defects. It measures the response to small light stimuli that are presented in random position on a black monitor screen for 150 ms. The stimulus is presented at 500 different positions within a period of about 20 minutes. The ‘PeriForm’ program tests the patient’s ability to recognize simple form (lines of different orientation, letters or figures) in different areas of the visual field. A session consists of 250 presentations at different positions in randomized sequence. The examination takes about 15 minutes. The ‘PeriColor’ program assesses discrimination of broad colour categories in the visual field. It is very similar to PeriForm except that coloured squares are used as stimuli.

HRP is performed in a dark room and the head of the subject is stabilized with a chinrest. In the initial studies, a 14” monitor was used, later replaced by a 17” monitor to permit a more detailed assessment.

The HRP programs allow the use of different stimuli (e.g., differences in size), plus a change in background luminance. Furthermore, the stimulus duration and the intervals between stimuli can be changed according to individual abilities. This set of programs allows the assessment of visual field size with a much higher spatial resolution and flexibility than commercially available devices. The main advantage of this procedure is the possibility to perform a detailed analysis and to provide accurate information on the functional status.
**Figure 1.** Visual field size and training area. The first column shows the result of the perimetry, left and right eye were tested separately. Each circle represents the visual field of each eye up to 60° eccentricity, black indicates blind areas, shaded parts represent fields of inadequate vision and white sections represent intact areas. The second column displays the four possible monitor positions in relation to the visual field squares. The circle shows the binocular visual field, the small grey square is the area that was trained. The last column shows the result of the PERIMAT program in the trained area before and after training. Modified from Kasten and Sabel (1995).
of specific areas of the visual field. In this way, for each patient, areas with residual function are detected.

For each task, a corresponding version of the program is available for training of that particular function. The VISURE program has been developed to train at the border between the intact and the deficient sectors. In the SEE-TRAIN program, the patient has to detect a stimulus on a black screen. The brightness of the stimulus changes from dark grey to light white in the same position. The FORMTRAIN program is a discrimination training program for recognizing several geometrical figures (squares, circles or triangles). The COLORTRAIN program trains the capabilities of colour perception in damaged visual areas. The FIXTRAIN program includes several procedures for patients with inadequate fixation.

After the areas with residual function are determined, the patients receive a disk to use at home with the software adapted to their respective deficit and they are instructed to train for 1 hour every day in a dark room. The results of every session are saved on disk for subsequent analysis. As soon as the patient reaches a pre-determined level of performance (more than 90% correct responses) the program advances to a more sophisticated level where stimuli are presented further out in the blind visual field section. The therapy program has two different sounds as a feedback to let the patient know whether the reaction was successful or not.

3. Results of the First Studies

All the studies discussed in this review are reported in Table 1.

Using a computerized training program (Vision Restoration Therapy — VRT), Kasten reported in 1995 the results of a pilot trial in patients with homonymous visual field deficits due to central brain damage. Eleven patients were trained at home for 1 hour per day for a total of 80–300 hours. The results of the experimental group were compared with those of three patients who opted not to participate in the training procedure or those with fewer hours of training. The trained group showed a reliable enlargement of visual field size. This was revealed by a significant improvement in the detection of small light stimuli, an increase in the ability to discriminate colours and a minor, but noteworthy, improvement of shape discrimination in the blind areas of the visual field (Kasten and Sabel, 1995).

Although several studies have reported partial recovery after extensive training of residual function in humans (Bien et al., 1999; Kreutz et al., 1999; Sabel and Aschoff, 1993; Sabel et al., 1997), the results were not always positive. This meant there is a possibility that partially damaged areas of the visual system may be the elements from which visual function recovery can start. However, factors inducing visual improvement have not been defined. There-
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Visual field defect</th>
<th>Site of lesion</th>
<th>Training methodology</th>
</tr>
</thead>
</table>
| Kasten and Sabel (1995)| 14                 | Homonymous visual field deficit | 10 stroke of the posterior cerebral artery  
2 tumour operation  
1 post-traumatic damage  
1 cerebral haemorrhage  
14 stroke/cerebral haemorrhage/insufficient blood circulation  
9 trauma or brain surgery  
4 cerebral inflammation | VRT                  |
| Kasten et al. (1998a) | 27                 | Homonymous visual field deficit |                                                                                   | VRT                  |
| Kasten et al. (1998b) | 19                 | No specified visual field deficit | Optic nerve injury  
(traua/neuropathy/other)  
Post-chiasmatic injury  
(traua/stroke/other) | VRT                  |
|                        | 19                 |                         |                                                                                   | VRT                  |
| Kasten et al. (2001)  | 22                 | 11 homonymous visual field defect  
11 heteronymous field defect | 6 stroke/cerebral haemorrhage/insufficient blood circulation  
8 trauma/brain surgery  
8 cerebral inflammation/other  
11 ischemic  
4 brain surgery  
2 brain haemorrhage | VRT                  |
<p>| Reinhard et al. (2005)| 17                 | Homonymous visual field deficit |                                                                                   | VRT                  |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Visual field defect</th>
<th>Site of lesion</th>
<th>Training methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kasten et al. (2006)</td>
<td>15</td>
<td>Homonymous visual field defect</td>
<td>Cerebral lesions: 5 stroke, 3 trauma, 1 meningencephalitis, 6 surgery/haemorrhage/hypoxia</td>
<td>VRT</td>
</tr>
<tr>
<td>Gall et al. (2006)</td>
<td>15 (6 months training), 9 (12 months training)*</td>
<td>No specified visual field defect</td>
<td>Stroke/traumatic brain injury (TBI)</td>
<td>VRT</td>
</tr>
<tr>
<td>Mueller et al. (2007)</td>
<td>95 complete hemianopia, 102 incomplete hemianopia, 43 quadrantanopia, 6 scotoma, 48 diffuse defect, 8 tunnel vision</td>
<td>214 stroke, 43 trauma, 34 tumour, 5 arteritic anterior ischemic optic neuropathy (AION)</td>
<td>VRT</td>
<td></td>
</tr>
<tr>
<td>Gudlin et al. (2008)</td>
<td>5</td>
<td>No specified visual field defect</td>
<td>5 primary open angle glaucoma, 20 primary open angle glaucoma, 5 normal tension glaucoma, 4 secondary glaucoma, 1 angle closure glaucoma</td>
<td>VRT</td>
</tr>
<tr>
<td>Sabel and Gudlin (2014)</td>
<td>30</td>
<td>Visual field defect (mild, moderate and severe)</td>
<td>5 primary open angle glaucoma, 20 primary open angle glaucoma, 5 normal tension glaucoma, 4 secondary glaucoma, 1 angle closure glaucoma</td>
<td>VRT</td>
</tr>
<tr>
<td>Study</td>
<td>Number of subjects</td>
<td>Visual field defect</td>
<td>Site of lesion</td>
<td>Training methodology</td>
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</tbody>
</table>
| Jobke et al. (2009) | 8                  | Variable visual field defect | Group 1: 4 ischemia  
4 injury/tumour/stroke/surgery  
Group 2: 4 ischemia  
2 injury  
2 surgery  
1 stroke  
1 meningitis | Extrastriate VRT/VRT  
VRT/extrastriate VRT |
|                     | 10                 |                           |                                                                               |                            |
| Bola et al. (2013b) | 53                 | Variable visual field defect | Prechiasmatic: 13 (AION)  
7 optic nerve inflammation  
6 idiopathic optic nerve atrophy  
5 tumour  
4 retinal artery occlusion  
2 non-arteritic anterior ischemic optic neuropathy (NAION)  
2 glaucoma  
2 trauma  
12 others  
Postchiasmatic: 83 stroke  
5 trauma  
4 tumour  
6 others | HRP evaluation***    |
|                     | 98                 |                           |                                                                               |                            |
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Visual field defect</th>
<th>Site of lesion</th>
<th>Training methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabel et al. (2013)</td>
<td>23</td>
<td>Hemianopia</td>
<td>23 stroke</td>
<td>VRT</td>
</tr>
<tr>
<td>Gothe et al. (2002)</td>
<td>45</td>
<td>10 acuity &lt; 20/400</td>
<td>Prechiasmatic lesions</td>
<td>TMS</td>
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<td></td>
<td></td>
<td>15 perception of movement or light</td>
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<tr>
<td></td>
<td></td>
<td>10 no residual vision</td>
<td></td>
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<td></td>
<td></td>
<td>10 control group</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>No specified visual field defect</td>
<td>Optic nerve lesions</td>
<td></td>
</tr>
<tr>
<td>Sabel et al. (2011b)</td>
<td>22</td>
<td></td>
<td></td>
<td>12 tACS</td>
</tr>
<tr>
<td>Fedorov et al. (2011)</td>
<td>446</td>
<td>30% contraction of the peripheral</td>
<td>Optic nerve lesions:</td>
<td>10 placebo stimulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>border</td>
<td>209 traumatic brain injury</td>
<td>rtACS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24.4% central or paracentral</td>
<td>134 inflammation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>scotoma</td>
<td>40 brain tumour</td>
<td></td>
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<td></td>
<td></td>
<td>26.9% scotoma and peripheral</td>
<td>63 vascular lesion</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>contraction</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>18.7% residual island of vision</td>
<td></td>
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</table>

* In this study the authors specified a different period of training as they compared results obtained after six and twelve months. The usual training time was six months.

** Six patients with bitemporal field defects were counted once only in the analysis of demographic data but twice for analysis of visual performance.

*** These patients have been evaluated but not trained.
fore in 1998 Kasten studied 27 patients with homonymous visual fields defects due to cerebral lesions in order to better understand the potential of residual visual function in patients with cerebral blindness. For each patient, data from five consecutive campimetric measurements were superimposed with the HRP and the number of correctly recognized stimuli ('hits') in the defective area was calculated. Perimetry with the Tübinger Automated Perimeter and computer-based perimetry showed congruent results. The overlapping of five consecutive campimetric tests (Fig. 2) led to the identification of three zones: the blind zone, the intact zone and the transition zone. The blind zone consists of the area, connected with an uninterrupted line, in which the probability of stimulus detection in all positions is $\leq 20\%$ (zero or one stimulus detected in five consecutive tests). This line was then used to define one border of the transition zone. The intact zone consists of the area in which the probability of stimulus detection in all positions is $\geq 80\%$ (four or five stimuli detected in five consecutive tests). The uninterrupted line connecting points with four or five hits provided the second border of the transition zone. The transition zone consists of the area in which the probability of stimulus detection in all positions is between 20% and 80%. It is usually located between the blind and intact zones of the visual field (Kasten et al., 1998a). According to the authors, the transition zones would be the functional representation of diffuse neuronal structure that had survived after the primary injury and could be the neurobiological substratum for visual function recovery. In fact, according to
the 'minimum residual structure' hypothesis, the survival of 10–15% of the neurons should be sufficient for the recovery of visual function (Sabel, 1997).

The positive results of the pilot study, despite its methodological limitations, led to the launch of two independent, placebo-controlled clinical trials in patients with visual field defects due to visual cortex or optic nerve damage. The comparison of the results of the two different groups of patients was reported by Kasten and colleagues in 1998 (Kasten et al., 1998b). The aim of this study was to determine whether visual improvements could be achieved even beyond the time window of spontaneous plasticity, characterized by possible partial functional recovery, which can be seen within 4–6 months from the time of injury. Patients were randomly assigned to an experimental (VRT) or a placebo group (foveal fixation training only). The restitution training consisted of a PC-based training program that the patient performed at home for one hour per day over a period of six months. During this time several thousand visual stimuli were presented systematically on the computer monitor, so that stimulation of areas of residual vision located between the intact and the blind visual field sectors, the so-called 'transition zones', was achieved. The results of these two clinical trials demonstrated for the first time a significant reduction of blindness due to repetitive stimulation of the 'transition zones' of the visual field. Interestingly, the two groups of patients showed different levels and characteristics of improvement. Patients with post-chiasmatic injury showed a significant increase of visual field size amounting to 29.4% above baseline, corresponding to an average shift of the visual field border by 4.8° of visual angle. Unexpectedly, the training, which only included white or grey stimuli, also determined an improvement in colour and form recognition. In the group of patients suffering optic nerve injury, the training effect was even more pronounced. In fact, the visual field size increased by 73.6% over baseline, corresponding to an average shift of about 5.8°. Differently from the post-chiasmatic group, these patients showed improvement mainly in the early training phase, not only in the visual fields but also in visual acuity, while no effect was detected on form and colour perception.

The effects of VRT also extended to other neuropsychological functions that are of everyday use. In fact, trained patients showed improved performance in paper-and-pencil tests of visual exploration and attention, and more than 72% of patients reported subjective improvements in vision. The tests used were a paper-and-pencil form of the Stroop test and the AKT test. In the first one there are three different tasks with increasing executive function difficulties: first subjects read colour words, secondly they name colour plates, thirdly they name the colour of colour words printed in a different colour than indicated by the word. Time is measured for each trial and the difference between the second and the third task represent a measure of attentional interference. The AKT test is a visual search task with subjects marking tar-
get patterns in an array of distracter stimuli. Time to perform the test, number of missed stimuli and errors are measured (Poggel et al., 2008). Patients with visual field defects due to brain damage suffer from severe impairment of activities of daily life such as reading, driving, or overall orientation, and they have significantly lower vision-related quality of life values than patients with glaucoma or optic neuritis (Gall et al., 2008b). Several papers confirmed the improvements in vision and health-related quality of life metrics in patients trained with VRT (Gall et al., 2008a, 2009, 2010, 2011).

4. The Perceptual Learning Paradigm

The underlying neurobiological mechanisms for recovery were still unclear, but the hypothesis was that the training reactivates surviving neurons within the areas of partially damaged structures, that is, the transition zones or areas of residual vision that can be present in damaged visual cortex. The restitution training would strengthen synaptic connections, thus improving visual functions in previously blind or impaired areas of the visual field. Furthermore, Kasten proposed that the effect of the light stimulus in the visual restitution training on other visual functions, such as colour and pattern recognition, supports the 'bottleneck theory' of vision restitution (Kasten et al., 2000). This theory affirms that the training effects can be explained as a process of perceptual learning and increased processing of information by residual structures surviving lesions of the primary visual pathways that induces the creation of new synaptic networks between the surviving neurons and those neurons involved in those specific functions in other brain areas.

This theory was confirmed in 2001 when Kasten published data of a follow-up study after a training-free interval (minimum six, maximum 47 months) (Kasten et al., 2001). Sixteen patients of the original restitution group and six patients of the placebo group were re-examined. All patients had either post-chiasmatic damage causing a homonymous visual field defect or a lesion of the optic nerve resulting in heteronymous field defects. In HRP as well as with conventional automatic perimetry neither group showed a significant decline in the number of correctly detected stimuli after training was discontinued. These data confirmed the findings of other studies on patients undergoing training for aphasia, neglect or cognitive planning who found that, after a specific training period, even after discontinuing training, the improvements showed sufficient stability with no or only small insignificant decreases of the effect obtained (Alderman et al., 1995; Brindley et al., 1989; Burke et al., 1991; Diller and Riley, 1993; Schwartz, 1995).

Analysing the results in the VRT group, three different types of patients were identified. Type I showed an improvement during the therapy and a further increase of results during the training-free interval. Type II achieved an
increase due to training, but had a reduction of their visual field size thereafter. Type III was completely stable. The authors hypothesized that as a result of training many patients used the regained visual abilities in everyday life, inducing stability or even further improvements; other patients probably did not use their improved abilities in the areas of restored vision and this led to a decrease of visual functions after the end of training. These patients, Type II, might benefit from phases of refresher training to maintain a stable visual field enlargement. A later clinical trial with 24 patients confirmed the stability of the improvement achieved after VRT after an average period of 3.8 years (Gall et al., 2006).

5. Efficacy of Visual Training in Pre-Chiasmatic Lesions

In 2007, the results of a large clinical observational study which involved 302 patients undergoing VRT for a period of six months at eight clinical centres in central Europe were published (Mueller et al., 2007). For the first time, five patients with arteritic anterior ischaemic optic neuropathy (AION) underwent visual training. The results from this large clinical study confirmed the findings of the previous smaller controlled studies and showed faster reaction times in HRP after training. Patients with anterior ischemic optic neuropathy who were visually trained showed an average increase of 7% of visual detection in HRP. As the sample was large enough it was possible to determine that the efficacy of VRT was not influenced by age or sex of the patients, or aetiology or age of the underlying lesion. The size of the residual vision area was confirmed as the main factor for the outcome; in fact, patients with larger areas of residual vision had higher plasticity potential compared to patients with no residual vision as demonstrated since the first studies comparing pre- and post-VRT (Kasten and Sabel, 1995).

The overwhelmingly positive results obtained with restorative training in patients with optic-nerve damage led to the initiation of a small open pilot study in glaucoma patients (Gudlin et al., 2008). Glaucoma is a chronic eye disease characterized by damage of the optic nerve usually due to excessively high intraocular pressure. If untreated it can lead to optic nerve damage resulting in progressive, permanent vision loss, starting with unnoticeable blind spots at the edges of the visual field, progressing to tunnel vision, and then blindness. In a pilot trial with five patients suffering from primary open-angle glaucoma, VRT was performed over two periods of three months with sessions lasting 30 minutes twice daily. To determine the stability of VRT-induced visual field changes there was a three-month training-free interval between the two training periods. Perimetric testing was performed with HRP, standard white-on-white and non-conventional blue-on-yellow perimetry. The last technique allows an early detection of perimetric damage in glaucoma patients.
The cones S (the photoreceptor sensible at blue light) are the first anatomical structure to be damaged in these patients. After VRT restorative training, with HRP as well as with standard perimetry, but not with blue-on-yellow perimetry, a visual field enlargement was evident. It remained stable even after a three-month training-free period. The molecular mechanisms of restoration probably involve network-like intraretinal connectivity. Retinal interneurons such as horizontal and amacrine cells are part of lateral processing of light perception in the physiology of converging and diverging downstream information processing between the photoreceptors and ganglion cells. VRT would probably influence these pathways, stimulating those cells that usually remain silent after having lost their direct connectivity partners.

The results of this original pilot study confirm that visual system plasticity is maintained into adulthood and occurs, using specific training, even after peripheral ocular pathologies.

Encouraged by the results of these previous studies, Sabel and his group published the data of a prospective, double-blind, randomized, placebo-controlled clinical trial conducted in 30 patients suffering from different clinical types of glaucoma. The patients included in the treatment arm were treated with a variant of the classic VRT. The training consisted of luminance increment stimulus similar to perimetry, and the task was simple detection. Training was performed six days a week for three months and the duration was 30 minutes twice daily. The results showed that computer-controlled vision training significantly improves visual detection accuracy and temporal processing in glaucoma patients (Sabel and Gudlin, 2014).

6. Further Steps Towards Understanding the Underlying Mechanism

To verify the possibility of improving the effectiveness of VRT, Jobke and colleagues proposed the possibility of stimulating the visual system more intensely using a more powerful behavioural stimulation paradigm with the purpose of activating the extrastriate pathway (Jobke et al., 2009). This work hypothesis was closely linked to the phenomenon of blindsight, whose physiological substrate is precisely linked to the extrastriate pathways. Recent studies demonstrated the presence in humans of direct thalamo–V5 connections (Barbur et al., 1993; Schoenfeld et al., 2002a, b), which may explain why the perception of motion may remain intact within hemianopic areas (Zeki and Fytcne, 1998). In extrastriate VRT the size of the trained area became larger and the entire blind area was stimulated with a massive moving spiral to primarily address motion perception. In a crossover study conducted in 2009 on 18 patients with visual field deficit who had prior VRT experience, the improvement was almost twice as good after extrastriate VRT as after standard VRT.
In many patients perimetric improvements were associated with subjective improvements, but in other patients, there was apparently a mismatch: subjective improvements could be reported without visual field expansion and, vice versa, visual field expansion could not be perceived by the subjects. Bola hypothesized that the phenomenon of ‘sightblindness’ could explain the mismatch problem (Bola et al., 2013a). Several studies suggested that visual functions are impaired in the ‘intact’ ipsilesional visual field of subjects with homonymous hemianopia. In fact, in these patients the uninjured hemisphere, considered ‘intact’, exhibits marked perceptual deficits in contrast sensitivity, processing speed and contour integration in both post-chiasmatic and pre-chiasmatic patients (Bola et al., 2013b). The lesion-induced disturbance of interhemispheric interactions and consequently synchronization in the uninjured hemisphere might be the key mechanism.

The initial research showed that the size of residual vision areas is the only factor that has a notable influence on outcome and the self-organizing map chart analysis revealed that the vision restoration hot spots are not randomly distributed but are a function of the amount of residual activity in the immediate surround. Eighty per cent of the vision restoration hot spots should be located in the areas of residual vision and only 20% should be in depth in the blind field. To investigate the role of residual vision in recovery, HRP visual field charts of hemianopic stroke patients were analysed before and after six months of VRT and all local visual field regions with (‘hot spots’) or without restoration (‘cold spots’) were identified. Hot spots were typically located closer than four mm from the scotoma border in cortical coordinates. It has been suggested that lateral interactions, known to play a role in perceptual learning and receptive field plasticity, can also play a major role in vision restoration (Sabel et al., 2013).

7. Vision Restoration and Non-Invasive Alternative Brain Stimulation

In the last 10–15 years research has also moved towards possible alternative techniques that could be used for inducing visual restoration. Two of these have been used by the group: transcranial magnetic stimulation and repetitive transorbital alternating current stimulation (rTACS).

In the '80s and '90s some studies reported the use of the transcranial magnetic stimulation technique, which creates an intense magnetic field inducing the activation of specific brain areas (Cohen et al., 1997; Meyer et al., 1991). Gothe decided to use this technique in order to verify whether the visual cortex, after a long period of deafferentation, was still able to generate visual experience (Gothe et al., 2002). Thirty five subjects presenting visual deficits after a pregeniculate lesion underwent transcranial magnetic stimulation. Ten of them presented some residual vision (visual acuity 20/400), 15
only light or movement perception, 10 were completely blind. The authors observed that the stimulation produced phosphenes in all patients with residual vision, in 60% of subjects with only motion or light perception and in 20% of blind subjects. In these last two groups the phosphenes threshold was in the normal range but the area in which they could be elicited was significantly reduced. The results also showed that in the group of patients with residual vision the phosphenes were quantitatively similar to those perceived by controls but they were significantly less often located within the contralateral visual field. In blind patients phosphenes were only perceived by subjects who had prior visual experience. The researchers' conclusion was that magnetic stimulation was able to increase the activation of the parenchyma, therefore the production of phosphenes, probably inducing the excitement of residual islands of functioning neurons. The hypothesis was that the possibility to induce phosphenes is an indicator of residual function in the visual cortex but long-lasting deafferentation of the visual cortex probably causes a reorganization of the visual system that reduces the possibility to experience cortically elicited phosphenes.

In 2011 rtACS was used in patients with optical nerve lesions. Previous studies using EEG, VEP and PET techniques had shown that the rtACS protocol influences cerebral functioning both in cortical and subcortical systems. Using a multichannel device generating a weak current through the orbit (putting two electrodes on each closed eye) they applied, on 446 patients with optical nerve lesions (Fedorov et al., 2011; Sabel et al., 2011b), train stimulations of individually adjusted amplitude according to personal threshold for phosphenes and cutaneous sensation. The protocol consisted of 10 daily sessions each lasting 15 minutes per eye. The rtACS method has been used in conjunction with EEG. The authors found an improvement in visual acuity (VA) and visual fields (VF) connected with a change in specific EEG patterns. More specifically, patients showing an improvement in both VF and VA presented an increase in occipital alpha activity; patients showing only a VF enlargement presented an increase in occipital theta activity; non-responders presented an increase of delta activity in frontal and occipital areas. The mechanism underlying the changes in visual function and in cerebral activity is still unclear. rtACS apparently induces retinal cells to activate the striate cortex promoting the synchronization of visual networks (Gall et al., 2013).

8. Criticism

The Vision Restoration Therapy has not been universally accepted and has generated many controversies within the neuro-ophthalmology community (Pouget et al., 2012).
Three are the main topics of debate. One of the major criticisms refers to the perimeter techniques used. Indeed, three different types of perimeter were employed: High Resolution Perimetry, conventional perimetry (TAP) and Scanning Laser Ophthalmoscope (SLO). It was noted that Sabel and co-workers used the same software program for both treatment (VRT) and result analysis. When patients were examined before and after VRT with TAP no gain in visual field was found. The HRP does not allow an adequate monitoring of fixation. Indeed, during VRT, fixation is monitored by randomly changing the colours of a 0.75º fixation light from bright green to yellow and the subject must respond within 500 ms. However, colour transition is so easy to detect that it does not require foveal vision. Reinhart used a SLO in order to determine the border of absolute field defect before and after VRT and to monitor the fixation. In fact the SLO allows to simultaneously display the retina, the fixation cross and the stimuli on a video monitor for the examiner’s viewing. Seventeen patients with stable homonymous visual field defects before and after a six-month VRT period were examined with SLO. In none of the patients a significant objective visual field improvement was observed (Reinhart et al., 2005).

Horton (2005a) and later Plant (2005) believed that mean visual field recovery following VRT was due to the small saccades effectuated by patients in the direction of the defective visual field. Indeed the saccades constitute a spontaneous mechanism of compensation in patients with homonymous hemianopia (Pambakian et al., 2000).

A further study using a 2D-eye tracker in 15 subjects with homonymous visual field defects due to cerebral lesions showed that VRT had no effect on either the direction or the amplitude of horizontal eye movements during visual field testing. The authors found no increase but rather a decrease in eye movements after VRT (Kasten et al., 2006).

Eye movements always represent a possible source of variability in visual field diagnosis and artefacts cannot exclude the available experimental evidence in support of vision restoration.

Another topic of criticism is related to the explanatory mechanism. It has been postulated that the positive effects of VRT are due to stimulation of cortical plasticity. The hypothesis is speculative and still lacks sufficient confirmatory scientific data that could be provided by non-invasive functional magnetic resonance imaging (fMRI). Marshall et al. (2008) used fMRI to analyse brain activity before and one month after VRT in patients with right lateral homonymous hemianopia due to stroke. In these patients a modification of brain activity correlated with improved detection time in the border zone was detected, specifically at the level of the right and left anterior cingulate cortex, the right dorsolateral prefrontal cortex and bilaterally at the level of the basal ganglia. Furthermore, a positive correlation was also present at the level
of secondary and associated visual areas. Nevertheless, analysing the results of VRT, while considering the possible neuroplasticity, should not underestimate perceptual learning, a confounding factor that should be controlled by including a placebo group in studies (Horton, 2005b).

Some authors have argued that studies on VRT often lack proper identification of lesion histogenesis and accurate topography of post-geniculate lesions. These elements may be essential regarding both clinical description and potential therapeutic effect (McFadzean, 2006).

Finally, financial considerations likely tend to turn the scientific debate more bitter, as VRT is still an experimental procedure and patients are required to pay for the training software (in the order of thousands of euros) (Glisson and Galetta, 2007).

9. Conclusions

It has been quite difficult to synthesize almost 30 years of studies. We chose only some of them, the ones that in our consideration constitute milestones for the field.

The research carried out by Prof. Sabel and his group has shown that vision restoration is possible in patients with visual deficits even when the damage has occurred many years before. Interestingly, these results can be seen irrespective of the origin and the site of the lesion, pre- or post-chiasmatic, the age or the gender of the patients. The mechanism underlying the restoration is still unclear but visual stimulation appears to influence visual receptive fields, inducing reorganization of cerebral areas and generating new synaptic networks. This is also highlighted by the improvement in other neuropsychological and visual functions than visual fields, such as visual acuity, colours and shape perception and discrimination. Visual restoration can also have positive effects on everyday life, acknowledged by patients, and this further improves visual competences and the lasting of restoration over time.

Residual vision activation theory has changed our way of thinking about brain damage and the possibility of plasticity in adulthood, giving new insight into visual rehabilitation and brain potential for reorganization. Although the results reported by this group have been mainly positive, the described improvements were quite variable and we think that the extreme variability in the etiology of lesions might play a role in the restoration of vision. New studies, including fMRI and groups of more homogeneous lesions, might help to better define the mechanisms that lead to visual restoration. The studies analysed have shown no significant difference in visual restoration according to age but no studies have been performed on very young patients or infants. Although we know that children often present a lower level of collaboration, it might be interesting to verify the effect of visual training on young patients.
in order to understand whether stimulation at an early age can show different results.

References


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